Depression in memory clinic patients: prevalence, symptoms and validity of standardized depression scales

Thesis by

Anne-Brita Knapskog

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Department of Geriatric Medicine
Oslo University Hospital, Ullevaal
Oslo, Norway

Institute of Clinical Medicine
Faculty of Medicine
University of Oslo

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Oslo University Hospital

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Table of Contents

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List of papers

I. Knapskog AB., Barca ML., Engedal K. A comparison of the validity of the Cornell Scale and the MADRS in detecting depression among memory clinic patients. Dement Geriatr Cogn Disord 2011; 32:287-294.

II. Knapskog AB., Barca LB., Engedal K. Prevalence of depression among memory clinic patients as measured by the Cornell Scale of Depression in Dementia. Aging Ment Health 2013; DOI 10.1080/13607863.2013.827630

III. Knapskog AB., Barca LB., Engedal K. A comparison of the Cornell Scale for Depression in Dementia and the Montgomery-Aasberg Depression Rating Scale in a memory clinic population. Dement Geriatr Cogn Disord 2013; 35: 256-265.

IV. Knapskog AB., Portugal MG., Barca ML., Countinho ESF., Laks J., Engedal K. A cross-cultural comparison of the phenotype of depression as measured by the Cornell Scale and the MADRS in two elderly outpatient population. J Affect Disord 2013; 144: 34-41.

Summary

Background

Depression is one of the most prevalent behavioral and psychological symptoms in dementia. It may be the first symptom of dementia, but previous depression also may be a risk factor for later dementia. Depression is common at any stage of the dementia disorder, but the processes that initiate the development of depressive symptoms may be different in the early stages than in the late stages of dementia. The symptoms of depression are not always pronounced in dementia, and they may be misjudged as symptoms of dementia. Therefore, even though depression is common, it is still often underdiagnosed and undertreated. This has a great effect on the lives of the patient and their caregivers. Among other things, it leads to a faster development of dementia with increased admission to nursing homes and hospitals, increased mortality, reduced quality of life both for the patients and the caregivers and increased caregiver burden for the patients' family members.

Aims

One of the five aims of this project was to explore the prevalence of depression and depressive symptoms of clinical importance among outpatients being evaluated for cognitive impairment and dementia in a memory clinic. Therefore we first examined the validity of the two most commonly used depression scales in Norwegian memory clinics: the Cornell Scale for Depression in Dementia (CSDD) and the Montgomery-Aasberg Depression Rating Scale (MADRS) (paper I). Thereafter, we studied the prevalence of depression and depressive symptomatology using the CSDD to diagnose depression and describe its symptom load, and examined the risk factors associated with depression in this group of patients (paper II). We also wanted to study how these two scales correlate with each other (paper III). The fourth aim was to explore whether the correlation between the two scales was influenced by patients' factors (paper III). At last, we wanted to examine whether there were cross-cultural differences in the way we fill in these scales in Norway compared to Brazil (paper IV).

Methods

We used a cross-sectional design for all four sub-studies. The validity study (paper I) included 125 patients from the memory clinics at Oslo University Hospital (OUS) Ullevaal (97 patients) and Innlandet Hospital Trust (SI) (28 patients) that came for a diagnostic assessment. Of them, 20 patients were included when they came for follow-up (SI), while the others were

included at their first visit. The same patients were included in the cross-cultural study, along with 86 patients from a psychogeriatric outpatient clinic in Rio de Janeiro, Brazil (paper IV). The data analyzed for the publication of papers II and III was retrieved from a register of patients assessed in a standardized manner with a common research protocol at collaborating clinics in southern, eastern, and western Norway. This register was established in January 2009 and will continue to include patients until they have reached 5000 patients. Oslo University Hospital, Ullevaal (OUS) and Innlandet Hospital Trust (SI) supply the most patients to this register. The prevalence study included data about 1470 patients from the register that had been examined at 12 memory or outpatient clinics (paper II). The comparison study of CSDD and MADRS included 520 patients from the memory clinics at OUS (361 patients) and SI (159 patients) (paper III). Data from some patients reported in paper III were also included from a previous register of patients examined at the OUS, which used approximately the same protocol from 1990 until the new register was established.

Information on depression and depressive symptoms was collected from most patients at their first visit to the memory clinics. The CSDD and the MADRS were filled in blindly from each other based on information from the caregivers and patients, respectively. It is mandatory for clinics that are part of the register to fill in the CSDD. However, the use of the MADRS is optional, resulting in a much lower number of patients with MADRS results in the register. The research protocol of this study contained information about demographic variables, neuropsychological test results, results of a physical examination, blood samples and other biomarkers as computed tomography (CT), magnetic resonance imaging brain scan (MRI), single-photon emission computed tomography (SPECT), and cerebrospinal fluid markers (amyloid beta, total tau and phosphorylated tau) for some of the patients. Different dementia diagnoses were made using all available information for each patient with the use of international accepted diagnostic criteria. In Norway we used the International Classification of Diseases, tenth edition (ICD-10) criteria for dementia diagnosis, and the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) was used in Brazil. The Clinical Dementia Rating Scale (CDR) was applied to evaluate the severity of the dementia. In Norway we used the ICD-10 for research and in Brazil the DSM-IV criteria to diagnose Alzheimer's disease, vascular dementia, and Parkinson's Dementia. The Manchester-Lund criteria were used for frontotemporal dementia, and the criteria according to McKeith and co-workers were used for Lewy Body dementia. Mild cognitive impairment (MCI) was diagnosed using the Winblad criteria. The term subjective cognitive impairment

was used when neither the criteria of dementia nor MCI were fulfilled. Depression was diagnosed in the validity study (I) and the cross-cultural study (IV) using the ICD-10 criteria for research and the DSM-IV criteria.

Results

Paper I. In Norway, the cutoff with the best sensitivity and specificity for the CSDD to detect depression was 5/6, and for the MADRS the best cutoff point was 6/7, independent of which diagnostic criteria was used. According to the Receiver Operating Characteristic (ROC) analyses, the MADRS seemed better to distinguish depressed from non-depressed patients in the Norwegian sample of patients referred to dementia assessment in a special health care clinic.

Paper II. About half of the patients included in the paper had a CSDD score higher than five, while 37.5% of the patients had a score higher than seven, and 14.1% had a score higher than 12. We found the highest scores for the CSDD among patients with dementias other than Alzheimer's disease (AD), a history of previous depression, and greater impairment in the activities of daily living (ADL). The strongest factors associated with depressive symptoms in the logistic regression analyses were younger age, ADL impairment and previous depression with a Nagelkerke R-square between 0.12 and 0.15 for the different cut-off points.

Paper III. In Norway, the correlation between the two scales CSDD and MADRS was 0.36 for the whole group of patients, 0.22 for the group of patients with dementia and 0.48 for those without dementia. The correlation was not influenced by "patient factors." The principal component analyses disclosed four factors for the CSDD—mood, anhedonia, cyclic, and physical, and two factors for the MADRS—mood and anhedonia. The correlations between sub-syndromes of depression (mood and anhedonia) were not any better, and were even worse for the anhedonia subscale.

Paper IV. The prevalence of depression was about 40% among patients referred to memory clinics and included in this study, in Brazil and Norway. However, the mean score of the CSDD was 14.4 (SD: 8.9) in Brazil and 6.8 (SD: 4.9) in Norway ($p < 0\ 001$). For the MADRS, the mean score was 13.2 (SD: 12.1) in Brazil and 8.4 (SD: 6.8) in Norway ($p=0.02$). In the Brazilian sample, the best cutoff for the CSDD was 12/13 and for the MADRS it was 9/10, much higher than for the Norwegian patients as reported in paper I (see above). The differences were partly due to higher scores on every item in the two scales, particularly for the CSDD items. The only item on which the Norwegian patients had a higher score was multiple physical complaints.

Conclusions

The prevalence of depressive symptoms is high among memory clinic patients. The strongest factors associated with depressive symptoms are younger age, ADL dysfunction and previous depression. Even though MADRS seems a bit better detecting depression in memory clinic patients, both the CSDD and the MADRS are suitable as screening tools, but the correlation between the two scales is low. The scores on both scales were significantly higher in Brazil than in Norway even though the prevalence of depression was the same in the patients of the two samples, meaning that screening tools should be validated in the population where they will be used.

Sammendrag

Depresjon er en av de hyppigste psykiske sykdommene som forekommer samtidig ved demens. Depresjon kan være første symptom på en begynnende demenssykdom, men tidligere depresjon kan også være en risikofaktor for en senere demensutvikling. Depresjon er i midlertidig hyppig i alle stadier av en demenssykdom, selv om det som utløser en depresjon i de tidlige stadiene kan være forskjellig fra det som utløser depresjon i de senere stadiene. Symptomene på depresjon er ikke alltid så uttalte, og symptomene kan bli misoppfattet som symptomer på demens. Så selv om depresjon er hyppig, blir den ofte ikke adekvat diagnostisert eller behandlet. Dette kan ha stor innvirkning på livene til både pasient og pårørende. Depresjon kan blant annet føre til en raskere utvikling av pasientens kognitive svikt og dermed raskere innleggelse i sykehus og sykehjem, økt dødelighet, redusert livskvalitet både for pasientene og deres pårørende og økt pårørende belastning.

Formål

Denne studien hadde fem formål. Et av målene var å undersøke forekomsten av depresjon og av klinisk signifikante depressive symptomer hos pasienter som var henvist til demensutredning ved en hukommelsesklinikk. Vi validerte derfor de to mest brukte depresjonskalaene i bruk ved norske hukommelsesklinikker: Cornell skala for depresjon ved demens (CSDD) og Montgomery and Åsberg Depression Rating Scale (MADRS) (artikkel I). Deretter studerte vi forekomsten av depresjon og depressive symptomer ved hjelp av CSDD, og undersøkte hvilke risikofaktorer som var assosiert med depresjon i denne pasientgruppen (artikkel II). Videre ønsket vi å undersøke hvor godt disse to skalaene korrelerer med hverandre og om noen faktorer hos pasientene påvirket denne korrelasjonen (artikkel III). Til slutt ønsket vi å undersøke om det var noen kulturelle forskjeller i hvordan depresjonsskalaene fungerer i Brasil og Norge.

Metoder

Studien var en tverrsnittsundersøkelse. I validitetsstudien (artikkel I) inkluderte vi 125 pasienter som kom for en demensutredning, fra Oslo universitetssykehus (OUS), Ullevål (97 pasienter) og Sykehuset Innlandet (SI), Sanderud (28 pasienter). Tjue av pasientene fra Sanderud ble inkludert da de kom til kontroll. Alle de andre ble inkludert ved første konsultasjon. De samme pasientene ble inkludert sammen med 86 pasienter fra en alderspsykiatrisk poliklinikk i Rio de Janeiro, Brasil i analysene som er presentert i artikkel

IV. Tallmaterialet for artikkel II og III ble hentet fra et register som inkluderer pasienter som kommer for demensutredning ved samarbeidende poliklinikker i sørlige, vestlige og østlige deler av Norge. Dette registeret ble etablert i januar 2009 og vil fortsette å inkludere pasienter inntil de har inkludert 5000 pasienter. Oslo universitetssykehus (OUS) og Sykehuset Innlandet (SI) er de to sykehusene som rekrutterer flest pasienter til dette registeret. Til prevalens studien inkluderte vi 1470 pasienter fra 12 poliklinikker (artikkel II). I korrelasjons studien mellom CSDD og MADRS inkluderte vi 520 pasienter fra OUS (361 pasienter) og SI (159 pasienter) (artikkel III). Opplysningene om noen av disse pasientene stammet også fra et tidligere register samlet på OUS. På OUS har man brukt omtrent samme forskningsprotokoll siden 1990 til det nye registeret ble etablert.

Informasjon om depresjon og depressive symptomer ble innhentet første gang pasientene kom til poliklinikkene for de fleste pasientene. CSDD og MADRS ble fylt ut avhengig av hverandre basert på informasjon fra pårørende og pasientene. I registeret er man pålagt å fylle ut CSDD, mens det er frivillig å fylle ut MADRS. Dette fører til at det er færre utfylte MADRS i registeret. Registeret inneholder opplysninger om demografi, nevropsykologiske testresultater, somatisk undersøkelse, blodprøver og andre biomarkører som CT, MR, SPECT, spinalvæskeundersøkelser (amyloid beta 42, total-tau og fosfo-tau) på en del av pasientene. Internasjonalt aksepterte demensdiagnoser ble satt, hvor all tilgjengelig informasjon ble brukt for hver enkelt pasient. I Norge brukte vi ICD-10 og i Brasil DSM-IV kriteriene for å stille en demensdiagnose og for subklassifisering av demens i henhold til etiologi, som Alzheimers sykdom (AD), vaskulær demens (VaD) og Parkinson demens (PD). Klinisk demensvurdering (KDV) ble brukt til gradering av alvorlighetsgraden av demens. Manchester-Lund kriteriene ble brukt for frontotemporal demens, McKeith kriteriene for Lewy-legeme demens og Winblad kriteriene for mild kognitive svikt (MCI). I de tilfellene hvor verken kriteriene for en demenssykdom eller MCI var til stede ble begrepet subjektiv kognitive svikt (SCI) brukt. I validitetsstudien (I) og i den sammenlignende studien mellom Brazil og Norge (IV) ble både ICD-10 og DSM-IV kriterier brukt til å sette depresjonsdiagnoser.

Resultater

Artikkel I. Skårene som samsvarte best med en klinisk depresjonsdiagnose var 6 eller mer på CSDD og 7 eller mer på MADRS. Dette var uavhengig av hvilke diagnosekriterier som ble brukt. MADRS var noe bedre til å skilte de deprimerte fra ikke deprimerte pasienter i våre analyser (ROC analyser) på pasienter henvist for en demensutredning i norsk spesialisthelsetjeneste.

Artikkel II. Halvparten av pasientene inkludert i denne artikkelen hadde en skåre på 6 eller høyere på CSDD. 37,5 % av pasientene hadde en skåre over 7 og 14,1% over 12. Vi fant høyest skår på CSDD blant pasienter med en demens av annen type enn AD, hos dem med tidligere depresjon, og hos dem med en svikt i dagliglivets aktiviteter (ADL svikt). Logistiske regresjonsanalyser avdekket at de faktorene som var sterkest assosiert med depressive symptomer var ung alder, ADL svikt og tidligere depresjon. Nagelkerke-R-square var mellom 0,12 og 0,15.

Artikkel III. Korrelasjonen mellom CSDD og MADRS var 0,36 for hele pasientgruppen og 0,22 for dem med demens og 0,48 for dem uten demens i artikkel III. Korrelasjonen ble ikke påvirket av andre faktorer hos pasientene. En faktoranalyse av CSDD resulterte i fire faktorer: emosjonell, manglende glede, syklisk, og somatisk. En faktoranalyse av MADRS resulterte i to faktorer: emosjonell og manglende glede. Korrelasjonen mellom sub-skalaene emosjonell og manglende glede var heller ikke noe bedre, for subskalaen manglende glede var den til og med verre.

Artikkel IV. Forekomsten av depresjon var ca. 40% hos pasienter henvist til hukommelsesklinikken inkludert i denne studien, både i Brasil og i Norge. På tross av dette var gjennomsnittlig CSDD skår høyere i Brasil (14,4, SD: 8,9) enn i Norge (8,4, SD: 6,8). P verdi < 0,001. For MADRS var gjennomsnittsskåren 13,2 (SD: 12,1) i Brasil og 8,4 (SD: 6.8) i Norge (p = 0.02). Skåren som samsvarte best med en klinisk diagnose var 13 eller høyere i Brasil for CSDD og 10 eller mer for MADRS. Dette var mye høyere enn i den norske gruppen (Se artikkel I). Forskjellen mellom de to gruppene var delvis forårsaket av høyere skår på de ulike spørsmålene i skalaene. Dette gjaldt spesielt for CSDD. Det eneste spørsmålet hvor den norske gruppen skåret høyere var på spørsmålet «fysiske plager».

Konklusjon

Forekomsten av depressive symptomer er høy hos hukommelsesklinikkpasienter. Depressive symptomer er sterkest assosiert med ung alder, ADL svikt og tidligere depresjon. Selv om MADRS synes å avdekke depresjon noe bedre, er både CSDD og MADRS egnet til screening av depressive symptomer. Korrelasjonen er derimot lav. Brasilianske pasienter skåret signifikant høyere på begge skalaene i forhold til de norske pasientene, selv om forekomsten av depresjon var den samme i begge grupper. Det er derfor viktig å validere skalaer i den befolkningen hvor de skal brukes før de tas i bruk.

Abbreviations

AD	Alzheimer's disease
ADL	Activities of Daily Living
AUC	Area Under the Curve
BDI	Beck Depression Inventory
BPSD	Behavioral and Psychological Symptoms of Dementia
CDR	Clinical Dementia Rating
CSDD	Cornell Scale for Depression in Dementia
CT	Computed Tomography
DLB	Dementia with Lewy Bodies
DSM-IV	Diagnostic and Statistical Manual for mental disorders 4th edition
ECT	Electroconvulsive Treatment
EOD	Early-Onset Depression
FTD	Frontotemporal Dementia
GDS	Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale
HDRS	Hamilton Depression Rating Scale
ICD-10	International Classification of Diseases 10th edition
LLD	Late Life Depression
LOD	Late-Onset Depression
MADRS	Montgomery-Aasberg Depression Rating Scale
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophies
NCD	Neurocognitive disorders
NPI	Neuropsychiatric Inventory
PDC-dAD	Provisional Diagnostic Criteria for Depression in Alzheimer's Disease
PDD	Parkinson Disease Dementia
PET	Positron emission tomography

RCT	Randomized Controlled Trials
ROC	Receiver Operation Characteristic
RRS	Relative Rating Scale
SCI	Subjective Cognitive Impairment
SPECT	Single-photon emission computed tomography
VaD	Vascular Dementia
WHO	World Health Organization

1 Introduction

Dementia is a syndrome caused by a variety of brain disorders that has dramatic consequences for the persons that are affected, their caregivers and society. This condition leads to total helplessness and need for care around the clock. It is assumed that approximately 35.6 million people worldwide had dementia in 2010. The number is expected to rise to 65.7 million in 2030 and 115.4 million in 2050. This increase is caused by population growth and demographic aging, which will cause a greater increase of both old people and old people with dementia in low- and middle- income countries than in high-income countries, where the prevalence is already high. The increase is expected to be less in Europe than in North and South America and the Asia-Pacific countries. The higher prevalence of dementia is associated with increasing age and a higher prevalence in women than in men, particularly at an older age, see figure 1 (Prince et al., 2013).

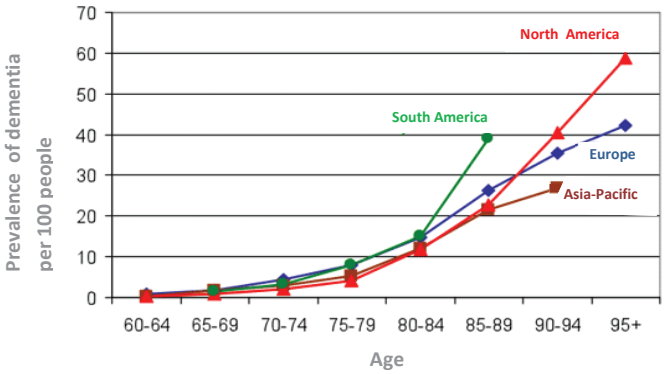

Figure 1.The prevalence of dementia across the world. Ajdusted from von Strauss et al., 2008

There are approximately 71 000 people with dementia in Norway, with that number expected to double in the next 35 years. More than 95% of the patients are older than 65 years, and while the prevalence among those aged 70-74 years is 5%, it rises to about 35% in the group older than 90 years (Engedal, 2002). It is estimated that 250 000 persons are affected by dementia, as each patient will have approximately three to four family caregivers. In Norway, approximately 39 000 people live in nursing homes (Kirkevold et al., 2012). From a representative study among nursing home (NH) patients in Norway, we see that about 80% of these patients have dementia, and dementia is the main reason for referral to institutional care

(Selbaek et al., 2007). Only 24% of the NH patients live in special care units designed for people with dementia (Kirkevold et al., 2012). The situation is very similar in Sweden, where the prevalence of dementia in nursing homes is approximately 75% (Svenskt demenscentrum). In the United Kingdom, one-third of the people with dementia live in care homes (which differ from Norwegian or Swedish NH in many ways), and about 64% of those living in care homes have dementia (Alzheimer's Society UK).

Dementia is not only a catastrophe for patients and their families, but it also has dramatic effects on society, because the costs associated with care will increase enormously because of the Norwegian welfare policy that gives priority to nursing home care for people with dementia. We do not know the exact costs, but one year in a nursing home is estimated to cost between 800 000 and 1 million NOK. It is estimated that the U.S. spends $157 billion-$215 billion, and the United Kingdom spends more than £17 billion annually for the costs associated with care for persons with dementia (Alzheimer's Society UK). In the U.S., 75% to 84% of the costs are caused by nursing home care and formal in-home care The expenses are expected to increase by nearly 80% per adult by 2040 because of an increased proportion of old people in the U.S. society (Hurd et al., 2013, Alzheimer's Society UK). These sums needed to provide proper care for people with dementia are comparable to, if not greater, than the costs for treatment of heart disease or cancer.

Dementia is a condition that affects the brain and causes cognitive, behavioral and psychological changes in the persons affected. Cognitive impairment is seen in all patients, and in nearly all cases there is a decline of cognition over time. Behavioral and psychological symptoms in dementia (BPSD) are very common, and previous studies have shown that as much as 80% of the patients will suffer from BPSD during the course of the disorder (Lyketsos et al., 2000). The presence and severity of the various symptoms will vary over time (Selbaek et al., 2013a, Wetzels et al., 2010).

One of the most prevalent BPSD symptoms is depression. Approximately 50% of the patients will suffer from depressive symptoms or depression during the course of a dementia disorder (Starkstein et al., 2005a). Depression may be the first symptom of dementia, but it is common in all stages of dementia. It may also be a risk factor for later dementia, but even though it is so common, it is still underdiagnosed and undertreated. There are probably many reasons for this—the symptoms of depression are not always very pronounced and some symptoms overlap with dementia. Detecting and treating depression may have a great influence on the

quality of life for the patient and his or her caregivers. It may postpone referral to hospitals and nursing homes, decrease morbidity and mortality, and in some patients decrease the progression of dementia. Finally, it has large economic consequences for the people involved and society.

There is no general agreement about the best method to evaluate and diagnose depression in dementia. This thesis is an attempt to find a suitable tool to screen patients who are experiencing cognitive impairment for depression. It is also an attempt to find the people with dementia that have the highest risk for developing depression.

1.1 Depression

1.1.1 Depression in the general adult population

Depression is one of the most common psychiatric disorders among adults. It is estimated that approximately 350 million people of all ages suffer from depression worldwide (WHO fact sheet N°369). In an epidemiological study performed in Oslo, the annually prevalence rate of major depression was about 7%, with a lifetime prevalence rate of nearly 20% in the adult population. The prevalence rate was more than twice as high for women than for men (Kringlen et al., 2001), which agrees with studies in other countries. Approximately 50% of the people with depression will have more than one episode of depression during their life span (Crown et al., 2002). Depression is an important contributor to the global burden of diseases and is a major cause of disability in all countries. It may lead to stress and dysfunction in the patient and worsen the life situation, and is also the major reason for the 1 million suicides committed every year (WHO fact sheet N°369).

Depression can be divided into three degrees—mild, moderate and severe. It is also useful to separate depression into two groups—those with manic episodes between the episodes of depression and those without manic episodes. These two conditions are often called bipolar mood disorder and unipolar mood disorder, respectively. In unipolar mood disorder (depression), the characteristic symptoms are depressed mood or sadness, loss of interest and joy, and reduced energy. Many depressed patients also have symptoms of anxiety, disturbed sleep, reduced appetite and feelings of guilt or low self-esteem, poor concentration or physical symptoms such as pain. The symptoms must last for at least two weeks to fulfill the criteria of a depressive episode according to the criteria of ICD-10. In bipolar mood disorder, the patient

also has a history of hypomanic or manic episodes. In the manic periods, the patients have an elevated or an irritated mood, are over-active, feel pressure to speak, and have an inflated self-esteem and a decreased need for sleep (WHO fact sheet N°369). Between the manic and the depressed episodes there are periods with a normal mood.

In addition to the unipolar and bipolar mood disorders, other subgroups of depression are defined. Dysthymic disorder is characterized by a persistent decreased mood for at least two years that is present more days than not, but the symptom load is not sufficient to fulfill the diagnostic criteria of a depressive episode. In psychotic depression, the patient has mood-congruent delusions or hallucinations, or both, combined with the signs of major depression. In adjustment disorder, depressed mood, tearfulness, or hopelessness occur within three months after the occurrence of a stressor. In this situation, bereavement (grief) is not considered a stressor. The condition can lead to great distress and/or disability. It should subside within six months if the stressor is removed. Otherwise the diagnosis is not correct (Alexopoulos, 2005). Bereavement causes a lot of suffering, but it should not be classified as depression. The two conditions could exist in the same person. If the two conditions occur together, the depressive symptoms and functional impairment tend to be more severe and the prognosis is worse compared with pure grief. A major depressive disorder secondary to bereavement tends to occur in people who are vulnerable to a depressive disorder.

Risk factors

Depression among adults is often accompanied by a personality disorder. Depression is also associated with a higher level of neuroticism and a family history of mood disorder (Bukh et al., 2011). Previous depression, drug addiction, somatic disorders, disability, and psychosocial factors such as lower education, stress, unresolved conflicts or financial worries, the loss of one or both parents before the age of 11, the loss of a partner, unstable relationships in marriage or other partnership, and the absence of a significant other are factors associated with depression at a younger age (Helsedirektoratet, 2009). Genetic factors play a more important role, but comorbidity is less important in depression earlier in life than in depression later in life. The genetic component involved in depression is very complex. There are multiple genes involved, and each gene has modest effect, but the genes interact with each other and the genetic components combined with environmental factors increase the vulnerability to both unipolar and bipolar depression (Lesch, 2004). Monogenetic inheritance is rare. Among others, gene variants with effect on the serotonin (5-HTT) system (5HTTLPR genes) play a role in depression. First-degree relatives of depressed individuals have a nearly

three-fold increased risk of developing a major depressive disorder, and heritability is estimated to be 40%-70% in unipolar depression (Lesch, 2004).

Diagnosis

There are two main classification systems in use that describe diagnostic criteria for depressive disorders—the International Classification of Diseases (ICD), developed by the Word Health Organization, first edition published in 1893 , and the Diagnostic and Statistical Manual of Mental Disorders (DSM), published for the first time in 1952 by the American Psychiatric Association.

The ICD criteria are the most commonly used criteria in Europe (including Norway). Version 10 is in use in clinical practice today. Separate criteria are developed for research (WHO, 1993). According to the ICD-10, the criteria for depression are divided into mild, moderate and severe, requiring the presence of at least four, six or eight symptoms respectively. The symptoms must be present for at least two weeks without any known manic episodes in the patient's life. The symptoms should not be due to substances or organic mental disorders. See Table 1.

The DSM criteria are more common in use in the U.S, because it was developed by the American Psychiatric Association. Version four was in use up to May 2013 (APA, 2000). The DSM-IV criteria for a major depression require a period of two weeks with depressed mood or loss of interest or pleasure in activities. Additionally, the patients must have at least four more symptoms (e.g., weight loss, insomnia, fatigue, concentration problems, and suicidal thoughts) present every or nearly every day. The criteria do not include symptoms that are related to medical conditions, mood-incongruent delusions or hallucinations and should not be due to effects of a substance. The symptoms should influence the social or occupational ability of the person. See Table 2.

Table 1. Diagnostic criteria for depressive disorder according to the ICD-10

A. General criteria

1. The depressive episode should last for at least 2 weeks
2. There have been no hypomanic of manic symptoms sufficient to meet the criteria for hypomanic or manic episode at any time in the individuals life
3. The episode is not attributable to psychoactive substance use or to any organic mental disorder

B. At least two of the following three symptoms must be present

1. Depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.
2. Loss of interest or pleasure in activities that are normally pleasurable
3. Decreased energy or increased fatiguability

C. An additional symptom or symptoms from the following list should be present, to give a total of at least four:

1. Loss of confidence and self-esteem
2. Unreasonable feelings of self-reproach or excessive and inappropriate guilt
3. Recurrent thoughts of death or suicide, or any suicidal behavior
4. Complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation
5. Change in psychomotor activity, with agitation or retardation (either subjective or objective)
6. Sleep disturbance of any type
7. Change in appetite (decrease or increase) with corresponding weight change

The depressive episode classified by degree:

- *Mild*. A total of at least four symptoms
- *Moderate*. Ta total of at least six symptoms
- *Severe*. All symptoms in B must be present and at least five symptoms from C must be present, to give a total of at least eight.

a) Severe depressive episode without psychotic symptoms: no delusions, hallucinations or depressive stupor

b) Severe depressive episode with psychotic symptoms: presence of delusions or hallucinations (not those listed as typically schizophrenic in criterion) or depressive stupor

Table 2. Diagnostic criteria for major depressive episode according to the DSM-IV-TR

A.	Five or more of the following symptoms have been present during the previous 2-week period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure. 1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful) 2) Markedly diminished interest and pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others) 3) Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day 4) Insomnia or hypersomnia nearly every day 5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6) Fatigue or loss of energy nearly every day 7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) 8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan of committing suicide
B.	The symptoms do not meet criteria for mixed episode
C.	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
D.	The symptoms are not due to direct psychological effects of a substance (e.g. a drug abuse, a medication) or a general medical condition (e.g. hypothyroidism)
E.	The symptoms are not better accounted for by bereavement (i.e. after the loss of a loved one), the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

The DSM-5 criteria were published in May 2013, and the new criteria for a major depression did not differ much from those of the DSM-IV (APA, 2013). The core symptoms are the same as in DSM-IV, but there are some small changes with regard to the additional symptoms that may be present. The diagnosis dysthymia is removed from the DSM-5, and this diagnosis is now included together with chronic major depression in the diagnosis of persistent depressive

disorder. Bipolar mood disorder and related disorders in DSM-IV are separated from the depressive disorders in different chapters in the DSM-5.

1.1.2 Late life depression (LLD)

Depression is common among the elderly, and the prevalence rates rises with increasing age (Luppa et al., 2012). When the first depressive episode occurs after the age of 65, it is called late-onset depression (LOD). The term "late life depression" (LLD) is also commonly used in the literature, including both those with LOD and those with previous episodes of depression earlier in life. Depression often affects elderly with chronic medical and neurological disorders, cognitive impairment, psychosocial adversity, or disabilities (Alexopoulos, 2005). Some authors claim that LOD is not caused by aging itself, but it is due to somatic diseases and disabilities due to somatic diseases (Grayson and Thomas, 2013, Wu et al., 2012). However, a general population survey in Nord-Trøndelag, Norway (the HUNT study), reported that the increase of depression with increasing age remained significant even after controlling for variables as socio-demographic variables and comorbidities (Stordal et al., 2001, Stordal et al., 2003). It is presumed that the prevalence of major depression in the general elderly population is 1%-4%, and 8% to 14% of the elderly population has clinically significant depressive symptoms. The prevalence rate doubles in people aged 70 to 85 years, which correlates with an incidence rate of up to 15% per year (Alexopoulos, 2005). In a review of 55 prevalence studies from 1990 to 2001, Rosenvinge and Rosenvinge found a prevalence rate of mild and major depression of 19% among the elderly in the general population. The prevalence was higher among patients in hospitals and nursing homes (32%) than among patients in primary care (18%) (Rosenvinge and Rosenvinge, 2003).

An increase in the prevalence rate of bipolar disorder is reported as well as an increase of elderly people with more severe and disabling episodes of depression and increased mortality. Dysthymia seems to be less prevalent. According to Devanand et al., dysthymia occurs in about 2% of the elderly population, and is associated with stressors such as isolation and long standing grief (bereavement) and cerebrovascular and neurodegenerative pathology. It is more prevalent in vascular dementia than in Alzheimer's disease (AD). People with dysthymia have a poorer response to treatment than elderly with other depressive disorders (Alexopoulos, 2005, Devanand, 2013).

The presence of comorbid diseases can make depressive symptoms difficult to recognize because depressive symptoms may overlap with physical symptoms such as loss of energy, poor concentration, and tiredness. Therefore, depression in the elderly is often underdiagnosed. In 1996, Cole and Yaffe reported that less than 20% of these patients were detected and treated (Cole and Yaffe, 1996). Factors that led to such a low detection rate were insidious onset of the symptoms, reduced insight in the patients, high age, and belonging to a minority group. Factors that increased the recognition of depressive symptoms in the patients were a history of mental disorder, low education or income, and widowed status (Cole and Yaffe, 1996). This review was performed before the introduction of the selective serotonin reuptake inhibitors (SSRIs). Newer studies found that depression is still under-treated among older people, even if more people today are treated with SSRIs than 20 years ago (Sonnenberg et al., 2008, Barry et al., 2012). In a nine-year longitudinal study of healthy community-living elderly (age above 70 years at baseline) published in 2012 by Barry et al, the increase of old people treated for depression was rather small compared to 20 years ago (Barry et al., 2012). During these years there has been a change in profile toward less use of antidepressants and more non-pharmacological therapy, but still the majority of depressed old people do not receive treatment. Even one-third of those with persistent depression do not receive treatment. In the study by Barry et al., treatment was associated with a higher intensity of depressive symptoms, higher education, worsening in cognitive status, belonging to the group of younger old and being physically frail (Barry et al., 2012). In a Swedish study of the oldest old (age above 85 years), a prevalence of depression of 24% was found. Of these patients, 58% were on antidepressant drugs (Bergdahl et al., 2011).

Symptoms

The phenotype of depression is very much the same in younger and older depressive patients (Hegeman et al., 2012). However, some authors found differences in the clinical features of depression across age-groups, with more expressed sadness and suicidal thoughts earlier in life, while anhedonia (failure to experience pleasure, interest and meaning in life), was more frequent among depressed persons later in life (Korten et al., 2012). Depression late in life may also have a heterogenic presentation and resemble a medical disorder (Alexopoulos et al., 2005).

Risk factors

LOD have different risk factors than depression earlier in life (early-onset depression, EOD). Depressed people with EOD have more personality disorders, higher levels of neuroticism

and a family history of mood disorders than people with LOD (Bukh et al., 2011). In a review and meta-analysis, Cole and Dendukuri found that five variables were significantly associated with depression among elderly living at home; bereavement, sleep disturbance, disabilities, prior depression in life and female gender. No specific comorbidity such as dementia or stroke or Parkinson's disease was identified; these three common disorders in old age are commonly seen as a comorbid disorders (Cole and Dendukuri, 2003). In the Swedish study of the oldest old, factors associated with depression were a higher number of medications with more analgesics and benzodiazepines, loneliness, inability to go outside and the recent loss of a child (Bergdahl et al., 2011). Compared to EOD, where psychosocial factors are of importance, LOD is influenced more by external risk factors. Disability, frailty, social isolation, relocation, caring for others, bereavement and low economic status may lead to depression in the elderly. The disabilities caused by comorbid diseases play a larger role in the presence of depression than the disease itself (Grayson and Thomas, 2013, Bukh et al., 2011, Korten et al., 2012).

Another important risk factor in EOD and LOD is related to coping. A recent review paper by Bjørkløf et al. reported a strong correlation between depressive symptoms among elderly people and their feeling of control in life. Coping and coping resources are important in the prevention of depression (Bjorklof et al., 2013).

Furthermore, 10-20% of surviving spouses develop depressive symptoms during the first year after their spouses' death. The symptoms persist if left untreated, and this kind of depression should not be seen as grief. However, it is not easy to separate the two conditions. Elderly people are more likely to develop depression-like symptoms than younger adults during the first months of widowhood. However, after two years there is no difference in the prevalence of depression across different age groups (Alexopoulos, 2005).

Psychosocial adversities, which may contribute to physiological changes, along with aging- and disease-related processes such as arteriosclerosis, inflammation, endocrine, and immune changes increase the risk for depression in the elderly (Alexopoulos, 2005). Such physiological and pathological processes may lead to dysfunction of the frontostriatal pathways, the amygdala and the hippocampus and an increased vulnerability of depression. A greater enlargement of the lateral brain ventricles and more white-matter hyperintensities are found in LOD. However, even if neurological changes could contribute, a direct lesion-depression association is unlikely because there is a heterogeneous clinical presentation and a

heterogeneous course of depression late in life. In addition, EOD may be a risk factor for LLD by contributing to brain abnormalities such as atrophy of the medial temporal lobes (including hippocampus) that predispose to depression (Alexopoulos, 2005).

Some special contributions of brain pathology of depression in old age.

The etiology of depression in late life is multifactorial, and both psychological and biological factors may contribute, see Figure 2. When it comes to biological factors, we have some evidence that degenerative and vascular changes of the brain, as well as immune and inflammatory processes, may lead to subcortical changes and contribute to depression. Furthermore, during depression the dorsal neocortical structures are hypometabolic and ventral limbic structures are hypermetabolic. An allostatic state (mediators of stress response are not inhibited) is found in patients with major depression, which induces an impaired immunity, a promoted arteriosclerosis, obesity, bone demineralization and an increase in atrophy of brain cells. An increased adrenocortical activity occurs, there are raised concentrations of IGF-1, and an initiation of inflammatory responses is found (Alexopoulos, 2005). Frontostriatal, amygdalar, and hippocampal dysfunction occur in some patients. This dysfunction makes people more vulnerable to depression and may explain an increased risk for chronicity and relapse.

Morphologically the same cortical and subcortical areas are involved in EOD and LOD, but the lesions and cognitive impairment are more pronounced in LOD. This may be due to different pathophysiological processes.

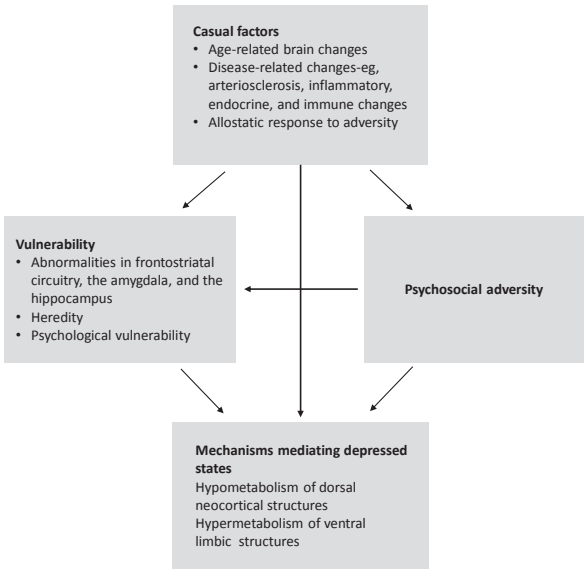

Figure 2. A model of late-life depression with brain dysfunction. Adjusted from Alexopoulos, 2005

Depression with executive dysfunction syndrome

Executive dysfunction is more common in late life depression than EOD, and is caused by dysfunction of certain parts of the frontostriatal circuitry. This may be due to subcortical disorders and white matter abnormalities. Disorders that compromise the frontostriatal pathways are often accompanied by depression. Executive dysfunction leads to more pronounced psychomotor retardation, apathy, and reduced interest in activities than in depressed patients without it (Alexopoulos et al., 2005). The patients' daily activities are impaired and they have limited insight and more vegetative signs (Alexopoulos, 2005). Depression with executive dysfunction resembles medial frontal lobe syndromes, and the dysfunction tends to persist after the depressive symptoms improve. However, depressed elderly with executive dysfunction also have classical symptoms of depression as sadness, hopelessness, helplessness, and worthlessness, and can meet the diagnostic criteria for major depression. However, the outcome is poorer. They often have a slower, poorer and more unstable response to antidepressants, and require more careful planning and follow-up (Alexopoulos, 2005, Alexopoulos et al., 2005).

Abnormalities of the amygdala

The amygdala is responsible for modulating mood states and integrating signals to centers responsible for coping behavior and autonomic activity. Disturbances of the connections predisposed to depression, and a decline in amygdala volume are seen in recurrent depressive episodes (Alexopoulos et al., 2005). Increased activity of the amygdala is associated with hypercortisolaemia and depression; an increase in activity results in inadequate inhibition of the structure by prefrontal centers (Alexopoulos, 2005).

The hippocampus is vulnerable to aging and aging-related changes and tends to lose substance with increasing age. It is vulnerable to ischemia and the effect of hypercortisolemia. A reduction of the volume is seen with major depression and this is correlated with a lifetime of depression (Sheline, 2011). Hippocampal abnormalities may predispose to depression (Alexopoulos, 2005, Alexopoulos et al., 2005).

Vascular or geriatric depression

Depression secondary to vascular disorders causing structural brain abnormalities is considered a separate subgroup often called geriatric depression. The symptoms of geriatric depression are often more severe and there is a higher prevalence of psychosis than in patients with early onset depression (Kessing, 2012). Cerebrovascular risk factors and disorders might predispose (Almeida et al., 2007), precipitate or perpetuate LOD. Patients with vascular disorders have a greater disability and cognitive impairment than those without. The most affected cognitive functions are verbal fluency and object naming. Symptoms such as apathy, retardation, and a lack of insight are more common than depression due to other causes. Less common are symptoms such as agitation and guilt. Prevention of cerebrovascular diseases might reduce the risk for vascular depression. Dopamine or norepinephrine-enhancing agents are favored in treatment of this form of depression because these agents promote ischaemic recovery. Alfa adrenergic blocking agents should be avoided (Alexopoulos, 2005).

Treatment

Some discrepancies concerning the efficacy of treatment of LOD compared to EOD are reported. Some authors found few differences in the treatment outcome between younger and older adults, at least if little comorbidity is present in the LOD patients (Grayson and Thomas, 2013, Alexopoulos, 2005). The main concern is that depression is underdiagnosed and undertreated in the elderly. In the Swedish study of the oldest old (above 85 years), approximately 50% the depressed patients were on antidepressant drugs, but half of these

were non-responders to treatment (Bergdahl et al., 2011). Antidepressants seem to be less efficient in older people with a short duration of illness. Patients with longer illness duration and moderate to severe depression seem to benefit more from antidepressants than those with a short illness duration and fewer symptoms (Nelson and Devanand, 2011). According to the Norwegian guidelines for treatment of depression, the first choice of treatment of mild depression should be counselling and psychological interventions. Antidepressants should be considered if the patient does not respond to these non-pharmacological interventions or if the patient has recurrent depression (Helsedirektoratet, 2009). A combination of psychotherapy and antidepressants should be considered in more severe cases of depression. The selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the first drugs of choice, followed by bupropion and mirtazapine. Treatment with antidepressants is mostly well tolerated (Alexopoulos, 2005, Alexopoulos, 2011), but has potentially serious side effects and potential interactions with other drugs. In a 2012 review, some studies showed that long-term treatment with antidepressants (SSRIs and the newer non-SSRIs) earlier in life decreased the risk of developing dementia, at least in patients with less severe depression. The same association was found in patients treated with lithium for bipolar disease (Kessing, 2012).

In psychotic depression, antidepressants should be combined with an atypical antipsychotic such as augmentation therapy (Alexopoulos, 2011). In addition, it is important to optimize the treatment of underlying illness or cease drugs with unfavorable side effects. Dopamine enhancing agents are the drugs of choice for depression with frontostriatal impairment.

Treatment with antidepressants should be continued for at least six months after remission. Recurrent depression should be treated with drugs for at least two years according to the Norwegian guidelines (Helsedirektoratet, 2009).

Electroconvulsive treatment (ECT) should be considered in the most severe cases, especially in patients with psychotic depression, when suicidal thoughts are present or the patients refuse to eat and drink (Alexopoulos, 2005). ECT has side effects such as retrograde amnesia and problems with learning new things, but in most cases these side effects are temporary.

Non-pharmacological treatment

Non-pharmacological treatments such as psychosocial interventions and psychotherapy may improve the outcome of depression in elderly individuals. Behavioral and cognitive therapy

(CBT) and interpersonal therapy (IPT) are the most popular; among elderly patients, both psychotherapies have shown the most positive results in RCTs. According to the Norwegian guidelines, structured psychological treatment should be offered at least 16-20 times over a period of six to nine months. Physical activity protects against depression and may reduce depressive symptoms in the less severe cases (Helsedirektoratet, 2009).

Recurrent depression

Depression in the elderly has a chronic or relapsing course in many cases (Cole et al., 1999). However, different studies showed contradictive results of how many elderly patients relapse. According to one article, two-thirds of the patients with a moderate to severe episode of depression experience recurrent depressions while only one-third do not (Kessing, 2012).

Prognosis

Depression is associated with poor well-being and increased mortality because depression is often underdiagnosed and inadequately treated in the elderly (Bergdahl et al., 2005). The prognosis of LOD is worse than for EOD. LOD increases the risk of somatic disorders such as cardiovascular diseases, it may worsen the outcome of many medical illnesses and it promotes disabilities (Alexopoulos, 2005). The decrease in function is comparative and even worse than that of adults with chronic somatic disorders. LOD increases the perception of poor health, and increases the costs of medical and health care services (Cole et al., 1999). Cole found that, after 24 months, one-third were well, one-third were still depressed and 21% had died (Cole et al., 1999). There is an association between higher mortality and late-onset major depression with executive dysfunction (Vilalta-Franch et al., 2013).

1.2 Cognitive impairment

1.2.1 Subjective cognitive impairment

Subjective cognitive impairment (SCI) is a term used when neither the diagnostic criteria for mild cognitive impairment (MCI) nor dementia are fulfilled, but the patient complains of declined cognitive performance. The diagnosis is used when one cannot prove a cognitive decline by neuropsychological testing, even though the person experiences cognitive problems, most with memory. SCI should not be difficult to distinguish from MCI, because there should be no objectively observed cognitive impairment as measured by one or more cognitive tests for the diagnosis of SCI. The test scores should be within the normal range

(less than 1.5 SD below the norm) for the person's age and education. Studies have shown that SCI could be associated with depressive and other affective symptoms (Studer et al., 2013, Buckley et al., 2013), and with chronic somatic morbidity, especially multi-comorbidity (Caracciolo et al., 2013). However, a follow-up study showed a 4.5-time higher risk for cognitive decline and an increased risk of subsequent AD (during 7 years) in the group with subjectively cognitive complaints compared to those without any cognitive complains (Reisberg et al., 2010). Another study confirms this finding (Dufouil et al., 2005). People with SCI who are concerned about their cognitive performance have the same risk for AD as MCI patients (Jessen et al., 2014). Especially among people with a high education, SCI may be the first sign of incipient AD (van Oijen et al., 2007). Therefore, we cannot absolutely exclude that the person with SCI has an incipient AD.

However, these studies have some limitations. Highly educated people will usually have normal scores on screening tests for dementia for a longer period than people with less education. Studies often use MMSE as a screening measure, but among highly educated people, MMSE is not a good instrument, because the results are influenced by education. Sometimes, when the MMSE result is within the normal range, the person is not subjected to further neuropsychological testing (van Oijen et al., 2007). Therefore, in the studies using MMSE as a screening tool, we cannot separate MCI patients from SCI or normal controls accurately. A recent review by Garcia-Ptacek et al. supports this statement. It showed that people with SCI as a group had lower scores on neuropsychological tests than people recruited from the general population, even after adjustment for age and education. The different cognitive performance between the people with SCI and people from the general population cannot be explained by psychiatric co-morbidity. A follow-up examination showed that the SCI group had a higher incidence of cognitive decline and AD than people from the general population (Garcia-Ptacek et al., 2013). Researchers have found an association between amyloid beta ($A\beta_{42}$) in cerebrospinal fluid (CSF) and memory performance among people with SCI and healthy controls, but unfortunately these people were not followed to see if they developed a cognitive decline or dementia over time (Rolstad et al., 2011). Similarly, cortical brain atrophy on MRI is seen in SCI and in people with amnestic MCI (Saykin et al., 2006). However, in a study by Saykin et al., the atrophy in SCI was not as pronounced as in MCI patients, but still significantly more marked than in the healthy control group. In another study including people with a SCI diagnosis and a control group matched for age and education, a functional magnetic resonance imaging brain scan (fMRI) revealed an increased

activation in the bilateral thalamus, caudate and posterior cingulate, left hippocampus and the parahippocampal gyrus in the SCI group compared to the control group with no subjective complaints when doing divided attention tasks. The results on the cognitive tests were the same in the two groups. The pattern of increased activity on fMRI was in the same regions as the decreased activity in AD patients during the divided attention tasks. The increased activity could represent an activation of compensatory processes that get lost with progression of the disease (Rodda et al., 2011).

1.2.2 Mild cognitive impairment (MCI)

Over the years, many terms with different definitions have been proposed to describe the stage between normal aging and dementia. Some 30 years ago it was believed that a significant decline in cognition was due to the natural decline of normal aging, and terms such as "benign senescence forgetfulness" (Kral, 1962), "age-associated memory impairment" (Crook et al., 1986) and "age-associated cognitive decline" (Levy, 1994) were proposed.

Today, mild cognitive impairment (MCI) is a term that describes a cognitive decline beyond what is expected for a person's age and education, and the decline should not be of a degree that the person fulfills the criteria for dementia. It may be described as the stage between normal cognitive decline due to the aging process and dementia. MCI is a vague diagnostic term and difficult to delineate from dementia. However, MCI is a very heterogeneous concept that may coexist with systemic, neurologic, or psychiatric diseases that will not develop to a dementia stage (Lopez, 2013). The term was first introduced in the late 1980s and the first attempt to make standardized criteria was done by Petersen and colleagues at the Mayo Clinic (Petersen et al., 1999, Petersen et al., 2001). The original Mayo criteria, which were first formulated in the late 1990s, proposed that people with MCI should have objective memory impairment for their age with neuropsychological test results equivalent to or below -1.5 S.D. of the mean when adjusted for age and length of education. The general cognitive function should be preserved, defined as neuropsychological test results for cognitive domains other than memory within 0.5 S.D. of the mean when adjusted for age and education. There should be no ADL dysfunction and the criteria for dementia should not be fulfilled. However, it was difficult to transfer the criteria concerning neuropsychological test results onto the individual level in clinical practice, and in 2004 the Mayo criteria for MCI were modified by an international working group to make them more applicable for clinical use (Winblad et al., 2004). According to Winblad et al., MCI may be divided into four subgroups according to

which cognitive domains are affected negatively: pure amnestic MCI, single non-amnestic MCI, multiple non-anamnestic MCI and combined with or without memory deficits MCI (Winblad et al., 2004). Amnestic MCI is defined as a clinically significant memory impairment that does not meet the criteria for dementia and non-amnestic MCI is a decline in cognitive functions other than memory, e.g., attention, language or visuospatial skills. Distinguishing between these subtypes of MCI may predict what type of dementia may evolve (if the condition progresses to dementia). In many cases, amnestic MCI is the phenotype of Alzheimer's disease in an early stage, but it is important to know that patients without memory deficits also can progress to AD. Memory deficits are not mandatory according to the new criteria suggested by National Institute on Aging-Alzheimer's Association (NIA-AA) for MCI due to AD (Albert et al., 2011). However, these criteria are not in use in daily clinical practice.

Textbox 1. MCI criteria according to Mayo and Winblad

The original Mayo criteria	The Winblad criteria

• Memory complaint, preferably corroborated by an informant
• Objective memory impairment for age
• Relatively preserved general cognition for age
• Essentially intact activities of daily living
• Not demented
	• Not normal, not demented (Does not meet criteria for a dementia syndrome
	• Cognitive decline
	  ○ Self and/or informant report and impairment on objective cognitive tasks and/or
	  ○ Evidence of decline over time on objective cognitive tasks
	• Preserved basic activities of daily living / minimal impairment in complex instrumental functions

Types of MCI • Amnestic MCI • Multiple domain MCI • Single nonmemory domain	Types of MCI • Amnestic MCI • Amnestic multidomain MCI • Single nonmemory MCI • Non-anamnestic multidomain MCI

The patient's level of education and age should still be considered when evaluating cognitive test results, and according to the Winblad criteria, the impairment should have progressed over a period of time to use the MCI diagnosis. Evidence of cognitive decline must be shown objectively over time with or without reported cognitive decline by the patient him/herself and/or by an informant. Basic activities of daily living should be preserved and complex instrumental functions (IADL) should be impaired only minimally or not at all (Winblad et

al., 2004, Albert et al., 2011). However, there are studies showing that the majority of MCI patients already have disabilities in IADL in the early stages of MCI with increasing prevalence of IADL impairment as the condition gets worse (if it is due to a dementia disorder) (Hesseberg et al., 2013, Perneczky et al., 2006, Gold, 2012). One of the earliest changes in IADL performance is the ability to manage finances—a strong predictor of conversion from MCI to dementia (Gold, 2012). Neuropsychological testing helps determine if a test result represents cognitive performance due to normal aging or a disease process. However, the best way to assess and define MCI is still controversial because there is still insufficient evidence to recommend specific neuropsychological tests or cutoff scores on various tests (Winblad et al., 2004). The concept of MCI is still under discussion, and among others, the European Alzheimer's Disease Consortium (EADC) has established their own working group to define MCI in a new way and find evidence for a strict definition that can be used in daily clinical work (Portet et al., 2006). The criteria of the EADC working group are not very different from the Winblad criteria, so the question is open whether the EADC criteria has added to the knowledge of how to define criteria for MCI that can be used in daily clinical practice.

Prevalence

The prevalence of MCI in the general elderly population varies between 2-20% according to several studies. The single amnestic subtype has the lowest prevalence (2-4%), while the prevalence rises to 18-21% if all subtypes are included (Ganguli et al., 2004, Lopez, 2013). The incidence and prevalence of MCI are significantly higher in patients with depression than in patients without co-morbid depression. Patients with both conditions have more than twice the risk of developing dementia than those without depression (Geda et al., 2006). They also have a faster cognitive decline (Modrego and Ferrandez, 2004).

Prognosis

The course of MCI differs greatly between individuals, regardless of gender and age at onset. Studies have shown that patients with MCI are at high risk of developing dementia. In fact, MCI is often the first clinical picture of AD. The conversion rate to AD is 5% to 15% per year, compared to a 1-2% incidence per year in the adult U.S. population (Petersen, 2011). The rate of conversion to dementia varies largely from 2% to 31% a year between different studies (Bruscoli and Lovestone, 2004). In referral clinics (e.g., memory clinics with highly selected patients), a 10% to 15% conversion rate per year is reported, and 80% of the MCI patients have converted into dementia after approximately six years in such clinics (Petersen

et al., 1999, Tierney et al., 1996). Gifford et al. found that 41% of the MCI patients included from memory clinics had converted to dementia during a period of three years (3.0 +/- 1.6 years) (Gifford et al., 2013). In a review of 19 longitudinal studies published between 1991 and 2001, Bruscoli and Lovesome found an overall conversion rate of 10%, five times the expected incidence rate of dementia of people of the same age (Bruscoli and Lovestone, 2004). In a population-based study of people aged 65 years and older, more MCI patients than normal controls progressed to dementia, but less than was found in clinical studies (Ganguli et al., 2011). We presume that people referred to specialist clinics have a more advanced MCI than people included in population-based studies. These considerable differences in conversion rates from MCI to dementia may be explained by different diagnostic criteria for MCI and variations in the populations studied. Altogether, approximately 50% of all people with MCI will develop dementia, most due to Alzheimer's disease, which is also true for MCI patients with comorbidity (Lopez et al., 2007). Normalization can occur in 30% to 50% of people during 10-12 years follow-up, although 19% to 20% is a more conservative estimate according to some authors (Lopez, 2013, Ganguli et al., 2004, Manly et al., 2008).

Treatment

No medical treatment is available today for MCI. According to a recently published review that included randomized clinical trials (RCTs), no pharmacological or non-pharmacological intervention has proven effective for MCI patients (Cooper et al., 2013). Some studies of treatment with Cholinesterase inhibitors (ChEIs) have shown a modest improvement of cognition in patients with MCI (Salloway et al., 2004, Doody et al., 2010). However, these drugs neither prevent conversion from MCI to AD nor reduce the overall incidence of dementia (Cooper et al., 2013). According to a Cochrane review, ChEIs are associated with significant side effects in MCI patients (Birks and Flicker, 2006). ChEIs may increase the recurrence of major depression in elderly patients, presumably because of a cholinergic hypersensitivity to the depressogenic effect of cholinoceptive agents (Reynolds et al., 2011). Other medical therapies (e.g., Gingko biloba, Vitamin E, anti-inflammatory drugs) have not been proven effective either (Lopez, 2013, Cooper et al., 2013). Studies with Piribedil (a dopamine agonist), Nicotine patches and Haunnao Yicong (a Chinese herbal preparation) have been promising, but the results from these few studies have not been replicated (Cooper et al., 2013).

In an observational study, Kivipelto and her colleagues in Finland showed that vascular and lifestyle-related risk factors, especially in mid-life, are associated with later cognitive

impairment (Kivipelto and Solomon, 2008). Interventions in lifestyle factors and prophylactic pharmacological interventions may reduce the conversion from MCI to dementia or at least postpone the onset, but this hypothesis has to be proven by intervention studies. However, there is a lack of non-pharmacological intervention studies of good quality. Some studies with memory training, reminiscence, cognitive stimulation, recreation and social interactions have been promising, but only promising. Physical activity also has shown positive effects in preventing MCI and dementia or at least postponing dementia, but the evidence is not as good as it should be to recommend physical activity to all elderly people to prevent or postpone MCI and dementia (Geda et al., 2010, Cooper et al., 2013).

1.2.3 Dementia

Dementia is not a single disorder but a chronic and, in most cases, progressive syndrome due to several etiological causes. The typical symptoms are those connected to higher cortical functions such as memory and learning capacity, understanding and judgment, thinking, orientation and language. Consciousness is not affected. A reduction in emotional control, change in social behavior or motivation occur together or precede the cognitive decline. Higher cortical dysfunction is associated with a decline in intellectual function in general and the ability to execute the activities of daily living. The most common diagnostic criteria for dementia in Norway are the ICD-10 criteria. These criteria require the evidence of a decline in both memory and other cognitive functions to such an extent that it influences the activities of daily living a significant degree (WHO, 1993). See Table 3.

Table 3. Research criteria for dementia according to the ICD-10

I.	A decline in memory, especially for new information, objectively verified.
II.	A decline in other cognitive abilities as judgment, thinking, planning, organizing and abstraction.
-	Mild. The decline influence on the activities of daily living.
-	Moderate. The decline makes it impossible to function without help.
-	Severe. The decline makes continuously help required
III.	Preserved awareness of the environment
IV.	A decline in emotional control, motivation or a change in social behavior
-	Emotional lability
-	Irritability
-	Apathy
-	Coarsening of social behavior
V.	The condition should have been present for at least six month.

The other diagnostic criteria, the DSM-IV-Text Revision (DSM-IV-TR), were published by the American Psychiatric Association in 2000 (APA, 2000). It is a text revision of the DSM-IV, published in 1994. See Table 4.

Table 4. Dementia according to the DSM-IV criteria

A. Development of multiple cognitive impairments: A1. Memory impairment A2. Impairment in at least one other cognitive disturbances: a)aphasia b) apraxia, c) agnosia, d) disturbance in executive functions
B. The cognitive deficits in criteria A1 and A2 must 1. cause significant impairment in social or occupational functioning, and 2. represent a decline from a previous level of functioning
C. The dementia diagnosis should not be made if the symptoms occur exclusively during the course of delirium
D. The condition cannot be explained by other psychiatric disorders.

The DSM-5 was published in 2013, and a new concept has been defined (APA, 2013). Dementia, delirium, amnesia, and other cognitive disorders are now called neurocognitive disorders (NCD) in the DSM-5. Mild and major NCD subtypes are due to all types of dementia, HIV, traumatic brain injury, substance/medication-induced, prion, other medical conditions, Huntington's disease, multiple etiologies, or unspecified. The core features in NCD should be a cognitive dysfunction to distinguish these disorders from other mental disorders. Furthermore, there must be a decline from a previous level of functioning to diagnose a NCD. The underlying pathology and etiology may be determined resulting in subtypes of NCD. Dementia is now called a major neurocognitive disorder. Minor NCD was previously called "cognitive disorder not otherwise specified," which is comparable to MCI. See Table 5.

Table 5. Mild and major neurocognitive disorders according to the DSM-5

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of a significant decline in cognitive function, and 2. A documented substantial (major NCD) or modest (mild NCD) impairment in cognitive performance
B. Interfere with the independence in everyday activities.
C. The cognitive decline does not occur exclusively in the context of delirium.
D. The cognitive deficits are note better explained by another mental disorder.

As mentioned above, dementia is a term that covers several conditions that lead to global higher cortical brain dysfunction, loss of ADL-skills, changed behavior and finally death. The prevalence of the types of dementia varies among different population groups. In the older population, Alzheimer's Disease (AD) is the most common cause of dementia followed by vascular dementia. In the younger population (below age of 65 years), the proportion of patients with frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) is higher than the older population, and the proportion of patients with AD is lower. AD is still the most common cause of dementia in the group between 45 and 64 years of age, while the prevalence rates of different forms of dementia below the age of 45 is not well known.

Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most frequent cause of dementia; it is diagnosed in about 60% of patients with dementia (Engedal, 2002). In addition to the general criteria of dementia, AD is characterized by a gradual onset over months to years with a history of cognitive decline, most commonly amnestic symptoms, and at least in one other cognitive domain (e.g., language, visuospatial, executive dysfunction). There should not be evidence of any other subtypes of dementia (McKhann et al., 2011).

Clinical and neuropathological diagnostic criteria for AD

Years before the clinical symptoms appear in people with AD (how many we do not know for sure), the pathological process starts in the brain, see figure 3. The process normally starts in the parahippocampal region (entorhinal cortex), which produces symptoms such as memory

impairment and disorientation in time and room (Braak and Braak, 1991). The pathological criteria are deposition of amyloid beta (Aβ42) in plaques and tau protein in neurofibrillary tangles (Albert et al., 2011). As the deposition of amyloid beta and phosphorylisation of tau protein migrate to other parts of the cortex, impairments in several neuropsychological domains and activities of daily living develop. In addition, behavioral and personality changes appear. These pathological changes appear years before the clinical AD; therefore there is a discrepancy between clinical AD and pathophysiological AD. However, about 40% of the AD patients have comorbid Lewy body pathology as well, which could influence the clinical symptoms (Bertelson and Ajtai, 2014).

In 1984, a working group initiated by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) established criteria for the clinical diagnosis of AD (McKhann et al., 1984). These original criteria, based on clinical signs divided AD into possible, probable or definite AD. The criteria have been used widely, but a revision was needed because of the advances in the understanding of the pathological changes in AD. In 2009, the National Institute on Aging (NIA) and the Alzheimer's Association sponsored a series of advisory round table meetings and established three working groups. In 2011, new recommendations for the diagnosis of MCI due to AD (Albert et al., 2011), the diagnosis of dementia due to AD (McKhann et al., 2011), and definitions of a preclinical stage of AD were published (Sperling et al., 2011). In these new criteria, AD is still defined as a clinical diagnosis, but various biomarkers are included as important signs for use in research studies. The papers published by the various working groups of NIA said the criteria should be used in general healthcare without access to advanced methods, not just research studies.

In 2007, another initiative was made by the International Working Group for New Research Criteria for the Diagnosis of AD. The intention was to make new definitions and terminology of AD, including both clinical variables and "reliable biomarkers" of neuropathological changes. In 2010, these DuBois criteria were published based on a clinic-biological duality, aiming to diagnose a pre-dementia stage of Alzheimer's disease (Dubois et al., 2010). New terminologies were proposed: pre-dementia stage of AD or prodromal AD, AD dementia, typical AD, atypical AD, mixed AD, preclinical states of AD including asymptomatic at risk state of AD and presymptomatic AD. Recently there has been a discussion about whether these criteria are useful in daily clinical practice, where the patient group is much more

heterogeneous than in research studies. A lack of accuracy was found using Dubois criteria compared to clinical criteria (Oksengard et al., 2010).

Risk factors

The genetic contribution for the risk of AD is estimated to be 58% to 79%, and many gene variants can contribute (Gatz et al., 2006). However, the contribution of each gene is small in most cases. In many cases it is probably the combination of different genes that increase the risk the most, together with other underlying pathological changes in the brain as concurrent cerebrovascular disease (Ballard et al., 2011a).

The autosomal genetic mutations of AD, encoding amyloid precursor protein (APP), presenilin 1(PSEN1), and presenilin 2 (PSEN2) are known to lead to early onset dementia, but account for less than 1% of all patients with AD (Ertekin-Taner, 2010). Another gene (SORL1) is identified as causing late-onset AD, but more dominant mutations on genes may exist (Ballard et al., 2011a). In addition, several gene variants increase the risk for AD (risk genes), of which the e4 allele of the ApoE gene is the best known. The presence of one or two APOE ε4 alleles increases the risk for late-onset AD and early-onset AD (Genin et al., 2011). If two ε4 alleles are present, the chance of developing AD is more than 30 times higher than those with two ε3 alleles (Ertekin-Taner, 2010). This genetic risk factor is stronger among people of European origin, especially in Northern Europe. Except for ApoE, the majority of the most common candidate genes have a relative risk of 1.2-1.5 (Ballard et al., 2011a).

There are several midlife risk factors identified for AD (Kivipelto and Solomon, 2008). Hypertension, hypercholesterolemia, atherosclerosis and vascular disorders, obesity, high intake of saturated fat, low vitamin B12 and folate (with high level of homocysteine), and smoking in midlife all increase the risk of later AD. Low education is also associated with increased risk of AD. These risk factors are all possible to modify, and prevention in midlife may reduce the risk for AD or at least postpone the onset (Kivipelto and Solomon, 2008). See figure 3.

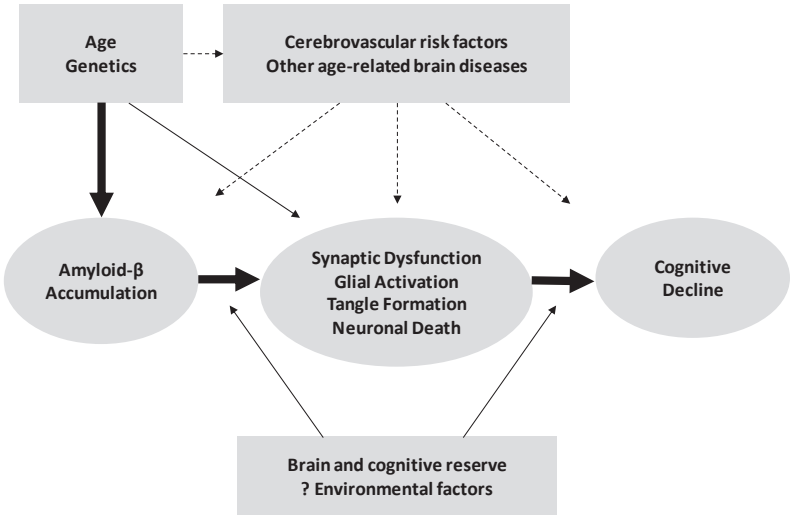

Figure 3. Hypothetical model of AD pathophysiological cascade. Adjusted from Sperling et al., 2011

Dementia with Lewy Bodies (DLB)

DLB is the second most common cause of neurodegenerative dementia in the elderly. Typical for this dementia disorder is that the memory impairment is neither the first and nor the most dominating symptom. More common are decline in attention, executive functions and visuospatial ability. To be diagnosed with DLB, the patient should have fluctuation in attention, visual hallucinations and/or parkinsonism. Many of the patients also have rapid eye movement (REM) sleep behavior disorder, autonomic dysfunction, are sensitive to antipsychotic drugs and have a low dopamine transporter uptake in basal ganglia demonstrated by a single-photon emission computed tomography (SPECT) or positron-emission tomography (PET) imaging (McKeith et al., 2005). SPECT imaging using ligands that bind to the dopamine transporter (DAT) may reveal decreased striatal DAT, and may be useful in distinguishing DLB from AD. Hypoperfusion (SPECT) and hypometabolism (PET) in the occipital lobe is also often found. Additionally, frontal and striatal hyperperfusion and parietal/temporal hypoperfusion may be seen. No specific abnormalities on MRI are found, but cerebral atrophy may be present (Bertelson and Ajtai, 2014). If DLB is not combined with AD, hippocampal atrophy is not present. In the ICD-10 and DSM-IV criteria, DLB is not a separate diagnosis. In the DSM-5, however, separate criteria are presented for major or mild NCD due to Lewy bodies.

DLB is neuropathologically defined as an alfa-synucleinopathy disorder such as Parkinson Disease Dementia (PDD) and multiple system atrophies (MSA). Lewy bodies (LB) are eosinophilic cytoplasmic inclusions of mostly alpha-synuclein in the brain. LB and dystrophic Lewy neurites are most often found in the brainstem, the limbic system and neocortex and more seldom the peripheral nervous system (McKeith et al., 2005, Morra and Donovick, 2013). The dementia should occur with or before the symptoms of parkinsonism. If the cognitive symptoms occur a year or more after the symptoms of the parkinsonism, the dementia is classified as Parkinson's disease with dementia (PDD) (Emre et al., 2007). The Parkinson plus conditions including multiple system atrophies (MSA) and progressive supranuclear palsy (PSP) cortico-basal degeneration (CBD) are different from DLB and PDD. The Parkinson plus conditions develop frontal dementia with dominating executive and visuospatial dysfunctions. The PSP and CBD are neuropathologically tauopathies (Lauterbach, 2004).

Risk factors

Few studies have explored the risk factors for DLB. The only known risk factors up to now were advanced age, male sex and a family history of dementia. A study combining data from three separate cohorts was published in 2013 (Boot et al., 2013). This study identified a risk factor profile that combined risk factors for both AD and PD. Known risk factors for PD such as non-use of caffeine, anxiety, depression and a family history of PD were also present in DLB. AD risk factors such as ApoE status and depression were also risk factors for DLB. The authors concluded with a close interaction between DLB, PD and AD.

Frontotemporal dementia (FTD)

FTD is a heterogeneous group of disorders that often affect persons in midlife, but also could occur among elderly people. Initially, memory and navigational skills and other aspects of general cognition are often spared (Neary et al., 1998, Warren et al., 2013). FTD can be divided into three syndromes: 1) the behavioral type with loss of insight and an extensive change in personality, including apathy, disinhibition, obsessions, rituals, stereotypies, and loss of executive skills; 2) progressive non-fluent aphasia with disturbance of the expressive language as the dominant feature, in some patients dominated with change in speech sound (phonemic) and in others as articulatory (phonetic, speech apraxia) errors or expressive agrammatism with terse telegraphic phrases; and 3) the semantic dementia (or aphasia) with an impaired understanding of word meaning and/or object identity (Neary et al., 1998, Warren

et al., 2013). Clinically, a variable overlap between the FTD syndromes and the Parkinson plus syndromes and motor neurone disease (MND) exists. In the ICD-10 criteria, FTD is classified as dementia in other specific diseases. The term Pick's disease is used, which was the original term for FTD. Now Pick's disease is only used in cases with specific pathology of Pick bodies. Pick bodies are intra-neuronal inclusions of randomly arranged filament of the tau protein (Takeda et al., 2012). In the DSM-IV criteria, FTD is classified as dementia due to other medical conditions, but the DSM-5 presents separate criteria.

FTD is a tauopathy characterized by a selective brain degeneration involving frontal or temporal lobes or both (Warren et al., 2013). Atrophy is seen on MRI. The sensitivity of structural MRI is highly variable (10% to100%), because the atrophy may vary a lot in extent and severity. The fluorodeoxyglucose positron-emission tomography (FDG-PET) has a higher sensitivity. Abnormalities including frontal, temporal, or frontotemporal hypometabolism are seen (Bertelson and Ajtai, 2014). In semantic dementia, there is a selective, asymmetric anteroinferior temporal lobe cortical atrophy and hypometabolism, predominately in the left hemisphere. In progressive non-fluent aphasia, perisylvian cortices in the dominant hemisphere mediating speech production are more affected (Warren et al., 2013).

Risk factors

Researchers found a substantial genetic component in the development of FTD. Six unrelated genes with more than 150 reported mutations are associated with FTD (Farlow and Foroud, 2013). About 25% of the cases of FTD are caused by mutations in three major genes located at chromosome 17 (MAPT and GRN) and 9 (C9ORF72). Mutations in the other three genes are rare. There is a stronger genetic association in the behavioral FTD. The semantic dementia seems to appear sporadically (Farlow and Foroud, 2013, Warren et al., 2013). Non-genetic risk factors are not known.

Vascular dementia (VaD)

VaD is a heterogeneous condition when it comes to etiology and symptoms. It may be seen secondary to stroke but also be due to chronic arteriosclerosis with hypoperfusion leading to subclinical brain injury and silent brain infarction (Gorelick et al., 2011). In a Norwegian study, 16% of patients with a first-ever stroke developed dementia (Ihle-Hansen et al., 2012). A large review from 2009 estimated that about 10% of the patients had dementia before their first overt stroke, and 10% developed dementia after their first stroke. If the patients had a

second stroke, more than 30% developed dementia (Pendlebury and Rothwell, 2009). The general criteria for dementia should be fulfilled to diagnose VaD. There should be a correlation between the clinical symptoms and the extent and localization of the vascular changes, and a correlation between dementia and the presence of cerebrovascular disease (Roman et al., 1993). Vascular dementia is a separate diagnosis in the ICD-10 criteria. An unequal distribution of the deficits in higher cognitive functions with some affected and others relatively spared is required. Clinically there should be evidence of focal brain damage and significant cerebrovascular disease etiologically related to the dementia. Vascular dementia is according to the ICD-10 divided into the subtypes: acute onset after stroke, multi-infarct dementia, subcortical vascular dementia, mixed cortical and subcortical vascular dementia, other vascular dementia and unspecified. In the DSM-IV and DSM-5 criteria, vascular dementia has its own individual criteria. There is a variation in the course of VaD—it may be static, remitting or progressive. Disturbances in gait, incontinence, changes in mood or personality, reduced psychomotoric speed, and executive dysfunction are frequently present but not specific for VaD (Roman et al., 1993).

There are many common risk factors for VaD, AD and stroke, as for AD and stroke, e.g. atrial defibrillation, hypertension, diabetes mellitus and hypercholesterolemia. A synergic effect between AD and cerebrovascular disease probably exists, which gives a mixed presentation between the two disorders (Gorelick et al., 2011).

Alcohol-related dementia (ARD)

Alcoholic dementia is caused by long term heavy drinking that damages brain cells or causes health problems that lead to brain damage. The typical impairments seen in ARD include deficits in abstracting abilities, short-term memory and disturbed verbal fluency, but no dysnomia or anomia (Oslin et al., 1998). Psychiatric problems are common in patients with alcohol-induced dementia. These patients develop apathy, irritability, and restiveness that results from damage to the frontal lobes. According to the classification of Oslin et al., the symptoms of dementia should persist at least 60 days after the last exposure to alcohol and be caused by direct neurotoxic effects. The consumption of alcohol should be at least 35 units per week for men and 28 units for women for more than five years. Dementia should be supported by the presence of other end-organ damage, ataxia or peripheral sensory polyneuropathy. Cognitive symptoms should stabilize or improve, and neuroimaging of ventricular or sulcal dilatation should improve with prolonged abstinence. Cerebellar atrophy,

especially of the vermis, also supports the diagnosis (Oslin et al., 1998). ARD is not a separate diagnosis in the ICD-10 criteria. In the DSM-IV criteria, there is an etiological subtype called alcohol-induced persisting dementia; it is called substance/medication-induced NCD in the DMS-V. Criteria for alcohol-induced persistent dementia in the DSM-IV include memory impairment and one or more of the following cognitive disturbances: aphasia, apraxia, agnosia, and/or disturbance in executive functioning. These deficits should cause significant impairment in functioning and represent a significant decline from a previous level of functioning. The deficits must not occur during the course of a delirium and must persist after the usual duration of substance intoxication or withdrawal. A patient history of abuse, physical examination, or laboratory findings that the deficits are etiologically related to the persisting effects of alcohol use can support the diagnosis. Compared to the classification of Oslin, there is no quantification of the consumption of alcohol or end-organ damage to support the diagnosis.

Wernicke-Korsakoff's Syndrome (WKS), which is related to nutritional deficiency of vitamin B1 (thiamine), is often seen among alcoholics after many years of alcohol abuse. It may be the chronic state after a Wernicke's encephalopathy, which is an acute state of alcohol intoxication. The typical clinical picture includes confusion, ataxia and ophtalmoplegia. WKS may also develop slowly after many years of malnutrition (Nardone et al., 2013). The most characteristic symptoms are profound retrograde and anterograde amnesia and confabulation. They often have normal long-term memory and other intellectual functions intact, at least in the early stages. The treatment is thiamine, but amnesia often remains after treatment (Nardone et al., 2013).

Treatment

Pharmacological treatment

The pharmacological treatments developed for dementia are developed for AD. There is still no treatment available that has proven to reverse, stabilize or slow down the course of AD. The drugs on the market have only modest and time-limited symptomatic effect and are not disease-modifying.

Five neurotransmitter-based drugs have been approved for clinical use for AD. Acetylcholinesterase inhibitors (AChEI) were approved for the American market in the beginning of the 1990s. They reduce the degradation of acetylcholine and thereby increase

both the level and duration of action at the nicotine receptors. The first drug, tacrine hydrochloride (Cognex®), had a short half-time and some serious side-effect (for instance hepatic toxicity), and is no longer in use. The three others, donepezil hydrochloride (Aricept®), rivastigmine tartrate (Exelon®), and galantamine hydrobromide (Reminyl®) are still in use, and have shown modest effect on cognition and function in patients with mild to moderate AD and Parkinson Disease Dementia (PDD), but not in vascular dementia (Honig and Boyd, 2013, van de Glind et al., 2013). The fifth drug in use is the N-methyl-D-aspartate (NMDA)-receptor antagonist, memantine hydrochloride (Ebixa®), which was approved in the U.S. in 2003. This drug inhibits the activity of another transmitter, glutamate, which may be toxic to the nerve cells in high doses. In studies, it has shown a modest symptomatic effect in moderate to severe AD, also as augmentative therapy together with AChEIs. When it comes to other drugs such as aspirin, steroids, NSAIDs, hormone replacement, gingko biloba, vitamins and dietary supplements, reviews have not found any good evidence for efficacy (Honig and Boyd, 2013, van de Glind et al., 2013).

For the treatment of Behavioral and Psychiatric Symptoms in Dementia (BPSD), cholinesterase inhibitors have only a modest effect according to a review from 2009 (Rodda et al., 2009). Antipsychotics have also shown a modest effect, but the use of antipsychotics is associated with serious side effects and increased mortality in this group of patients. If given, it should be given in low doses and for a short period of time. Due to the modest effects and potentially serious side effects, anticonvulsant mood stabilizer cannot be recommended according to a review from 2008 (Konovalov et al., 2008). In significant depression, antidepressants such as SSRIs and SNRIs may be effective, but the evidence for effect in mild cases of depression is not clear (Honig and Boyd, 2013, van de Glind et al., 2013).

Recently the goal has been to develop drugs that could modify the progression of AD. Efforts have been made to develop drugs that reduce the amyloid beta production (secretase inhibitors), inhibit the aggregation of amyloid plaques or derange them, and increase the clearance of amyloid beta via active or passive immunotherapy, or drugs that may prevent tau protein phosphorylation. None of these drugs have resulted in a demonstrably effective therapy (Honig and Boyd, 2013, Rafii, 2013).

Non-pharmacological treatment

The challenge in comparing non-pharmacological treatments is the lack of high quality studies. The heterogeneity of the non-pharmacological studies complicates the comparison of

the various interventions and comparison with "care as usual" (Woods et al., 2012, Carrion et al., 2013). Still, some studies have found modest effects on cognitive function using cognition-oriented approaches such as cognitive training, rehabilitation and stimulation. The effect is quite unstable and tends to disappear after the intervention is completed (Ballard et al., 2011b, Woods et al., 2012, Carrion et al., 2013). Some studies have also shown an effect on quality of life. These studies include studies with occupational therapies and exercise interventions which also slow down functional decline. There may also be an additive effect in combination with AChEI therapy. Brain training games have not been proven to benefit patients with AD (Ballard et al., 2011b).

In nursing homes, person-centered care (PCC) has been shown to reduce BPSD. Agitation, psychosis, and depressive symptoms were reduced after intervention with PCC. It also affected the quality of the patients' life (Rokstad et al., 2013).

Caregiver burden

Taking care of a person with dementia can be a burden. The symptoms and nature of the disorder demand a lot, and the consequences could be isolation and depression in the caregiver. As the disease progresses, the patients are in need of more support. In the U.S., approximately 75% of these patients are cared for at home by family members. In Norway, approximately 60% of the patients with dementia live at home with support by the family. In a meta-analysis, Pinquart and Sörensen found a strong association between behavioral problems of the patients and caregiver burden. This association was stronger than other stressors such as the patients' cognitive and physical impairment (Pinquart and Sorensen, 2004). In another meta-analysis, Pinquart and Sörensen found significant poorer health among caregivers in general than non-caregivers (Pinquart and Sorensen, 2003). The difference was particularly great between caregivers of patients with dementia and non-caregivers. An increased rate of depression has been reported in this group of caregivers (Pinquart and Sorensen, 2004). However, coping strategies influence the burden of care. Caregivers that think they are in control and use more active coping strategies are less depressed than caregivers who do not believe they are in control of their stressful situation. These caregivers use passive coping strategies with avoidance and are more burdened. Time spent with the patients and younger age of the patients is also associated with more burdens (Bruvik et al., 2013).

1.2.4 Biomarkers in MCI and AD

MCI is a clinical diagnosis. However, in research and in special clinical situations, biomarkers may play a role in identifying AD pathology in the heterogeneous group of MCI patients. Biomarkers have been shown to predict progression of MCI to dementia, to predict dementia due to Alzheimer's disease, and to increase the probability of MCI due to AD, especially when the patients have symptoms other than memory complaints (Albert et al., 2011, Lopez, 2013). Biomarkers may be divided into those detecting amyloid beta (Aβ) and those detecting neuronal injury. Examples of Aβ biomarkers are cerebrospinal fluid (CSF) amyloid β42 and positron-emission tomography (PET) amyloid imaging. One of the first pathological signs in AD is Aβ deposition in extracellular plaques in the brain. In CSF, lower levels of Aβ42 is measured as a sign of AD. Carbon-11 Pittsburgh Compound B (PiB) PET precedes structural changes in subjects with MCI, which indicates that the amyloid deposition occurs first, followed by neuronal loss (Jack et al., 2009). Biomarkers detecting neuronal injury of the brain are increased levels of total tau protein (t tau) and the more specific increased level of phosphorylated tau (p tau) protein that can be measured in CSF. Furthermore, reduced hippocampal volume or medial temporal lobe atrophy and amygdala can be seen on structural magnetic resonance imaging (MRI) as a biomarker for AD (van Rossum et al., 2010, Furney et al., 2011, Engedal et al., 2012a). Reduced brain glucose metabolism measured with fluorodeoxyglucose (FDG)-PET or reduced perfusion in temporoparietal cortex seen on single photon emission tomography (SPECT) may be useful as biomarkers for AD as well (Albert et al., 2011).

There are limitations in using biomarkers in MCI to predict dementia. First, there is a great variability in AD because negative CSF biomarkers do not exclude incipient Alzheimer's disease. Structural MRI may be difficult to interpret because of great variability with increasing age. Some research groups have found smaller hippocampal volumes in MCI patients compared to normal controls (Soininen et al., 1994); others do not (Laakso et al., 1998). There are few comparative studies comparing biomarkers with one another, and there are few studies that validate the biomarkers with postmortem examination. Most studies have included highly selected patients from second line memory clinics, and few studies have been carried out in unselected populations. There is little knowledge of which variables are of significant importance for the progression rate and time of progression to dementia. Also, little is known of the outcome when conflicting results of the validity of the biomarkers are reported. Biomarkers are not always clearly positive or negative. It is also important to know

that biomarkers are not specific; they can be seen in conditions other than AD, too (Albert et al., 2011, Lopez, 2013).

Another challenge in biomarker research is the overlapping of major brain pathologies. As much as 40% of AD patients also have severe cerebrovascular diseases, and nearly all patients with severe cerebrovascular diseases have substantial AD pathology, especially the oldest old (Heyman et al., 1998, Lewis et al., 2006). In addition, LBD and AD also often co-exist (Lim et al., 1999), and all three pathologies are seen in many old patients (Ince et al., 1995).

Inflammation

Recently there has been an increased focus on research to study the influence of the immune system and chronic inflammation on the pathogenesis of cardiovascular disease, multiple sclerosis, diabetes and cancer and major depression. Low-grade inflammation is also associated with changes in brain structure that could precipitate neurodegenerative changes associated with dementias (Leonard, 2007).

Cytokines

Cytokines are central in the hypothesis proposed to explain chronic inflammation. Cytokines are non-antibody proteins that can be produced by a wide range of cell types such as macrophages in the blood and microglia in the brain. These are cells that have the capability to phagocytate other cells, bacteria, small particles and more. Cytokines mediate intercellular communications. There are about 30 different cytokines, all with specific receptors on their surface. The release of cytokines is regulated through different mechanisms, and the result is a complex network involving feedback loops and cascades of immune response, for example. This response depends on synergistic or antagonistic actions and its various components. As a result of their pleiotropism, it is difficult to pinpoint the specific actions of individual cytokines (Wilson et al., 2002).

In AD patients, microglia has been found close to the amyloid plaques (Haga et al., 1989) and in CSF there are altered concentrations of cytokines involved in inflammation (Mattsson et al., 2009). Pro-inflammatory cytokines in the CSF correlate with the levels of tau and Aβ in patients with MCI who later progress to AD (Tarkowski et al., 2003). Studies have found activation of various pro-inflammatory markers in patients with AD of mild degree and in patients with MCI compared to elderly disease free controls (Tarkowski et al., 2003, Bermejo et al., 2008). Low-grade systemic inflammation also has been detected in the peripheral blood

of patients with late-onset AD (Zuliani et al., 2007), and higher peripheral immune activity is found in AD than in MCI patients (Parker et al., 2013). Such an activity is also found to predict conversion from MCI to AD (Diniz et al., 2010). Therefore, an inflammatory response may be an early biomarker in AD development and the changes in circulating markers are possibly related to the progression of AD (Leonard, 2007).

This pro-inflammatory state may also be a trigger to secondary pathological events. It may mediate synaptic dysfunction, mitochondrial dysfunction with activation of oxidative stress, and neurodegeneration (Medeiros et al., 2007, Cunningham et al., 2009). These biomarkers are still only used for research purposes.

Stress and cortisol

Furthermore, basal cortisol elevation has been shown to be associated with reduced hippocampal volume and memory impairment (Lupien et al., 1998). In one study, overnight urinary excretion of cortisol and cognitive function were measured in elderly people with no dementia disorder. They were followed-up after 7 years. Those with the highest cortisol level at baseline had the highest risk of cognitive impairment 7 years later (Karlamangla et al., 2005).

1.3 Behavioral and psychological symptoms in dementia (BPSD)

Recently the term "neuropsychiatric symptoms," (NPS) including both psychiatric and behavioral symptoms in dementia, has been used more, especially by neurologists. The concept "behavioral and psychological symptoms in dementia" (BPSD) is still preferred in Europe, and in the next version of the ICD criteria (ICD-11) the term BPSD will be used. This thesis will use BPSD.

BPSD occurs in the majority of patients with dementia at some time, and is part of the disease process. According to the ICD-10 criteria for dementia, a decline in emotional control, motivation or a change in social behavior is mandatory for the diagnosis of dementia. The prevalence rates measured with the Neuropsychiatric Inventory (NPI)(Cummings et al., 1994) are found to be about 60% among home-living people with dementia, and 70% to 95% of those with dementia living in nursing homes (Lyketsos et al., 2000, Zuidema et al., 2007, Wetzels et al., 2010, Bergh et al., 2012a, Selbaek et al., 2013b). Which of the symptoms that

are most prominent varies over time, but there is a tendency that the severity and prevalence of affective symptoms decreases and the behavioral symptoms, especially apathy and agitation, increase as the dementia disorder worsens. Agitation and apathy are most prevalent at the late stages of dementia (Zuidema et al., 2007, Wetzels et al., 2010, Selbaek et al., 2013a). A large Norwegian nursing home study where the patients were followed for 53 months found that as the BPSD fluctuated, apathy and irritability showed the highest, and hallucinations and euphoria showed the lowest cumulative prevalence rate (Selbaek et al., 2013a). A new symptom tends to appear when another disappears. In the beginning of the disorder, each type of dementia has its own characteristic BPSD-symptom (e.g., visual hallucinations in DLB, more depression in VaD, irritability in early AD, disinhibition in FTD), but as the dementia progresses there are different courses of individual BPSD, independent of the dementia type. The natural course of the symptoms may be difficult to predict. The patients are also more vulnerable to delirium with progression of the disease (Selbaek et al., 2013a).

Selbæk and Engedal performed a factor analysis of the NPI and found a four-factor solution: 1. affective symptoms including depression and anxiety; 2. psychosis including delusion and hallucination; 3.agitation including agitation and irritability; and 4. apathy as a stand-alone symptom (Selbaek and Engedal, 2012). These findings are almost in accordance with two other factor analyses of the NPIs (Aalten et al., 2003, Bergh et al., 2012a).

BPSD leads to an increase in the number of contacts with the health care services and an increase in the costs of care (Finkel, 2000). Agitation is associated with higher caregiver stress not only for family caregivers but also for the staff in nursing homes (Selbaek et al., 2013b).

The risk of nursing home placement increases with the BPDS symptom load. In a controlled intervention study of 18 years duration, intervention to reduce BPSD delayed nursing home placement by about 1.5 years. The caregiver's well-being improved. They had greater tolerance for the patient's memory and behavior problems, improved satisfaction with the support provided by family and friends, and fewer symptoms of depression (Mittelman et al., 2006). Depression is one of the most prevalent BPSD at least in the early stages of dementia.

1.4 Depression and MCI

The incidence and prevalence of MCI is significantly higher in patients with depression than in patients without depression (Geda et al., 2006). The persistence of depression in old people is associated with progression of MCI to dementia (Houde et al., 2008), and these patients often have more depressive symptoms early in the course of dementia as well (Garre-Olmo et al., 2003). Patients with MCI and co-morbid depression more than double the risk of developing dementia compared to MCI patients without depression, and they do also seem to have a faster cognitive decline. They also have a poor response to treatment with antidepressants (Modrego and Ferrandez, 2004). Depression in MCI may be considered a preclinical sign of dementia (Li et al., 2001), and the two conditions may be due to the same neurobiological processes (Heun et al., 2002). Some argue that there may be a continuum from late life depression through MCI and to dementia for a sub-group of patients (Panza et al., 2010).

A population-based cohort study of cognitively normal subjects with a follow-up time of 20 years reported that the severity of depressive symptoms at baseline predicted the time to development of MCI in APOE ε4 negative people, but not in APOE ε4 carriers (Dean et al., 2013). The explanation for this association is not known.

1.5 Depression and dementia

Risk factor for dementia or an early symptom of dementia?

Dementia and depression are two conditions that can coexist or be present separately. Depression earlier in life may be a risk factor for dementia (Jorm, 2001, Ownby et al., 2006), and a hospital study from Denmark found that the long-term risk of developing dementia increased 13% for each admission to hospital for depression or bipolar disorder (Kessing and Andersen, 2004). Similar findings were found in a community-based study (Dotson et al., 2010). A recent meta-analysis of population-based prospective cohort studies (mean follow-up 5 years) found that depression late in life was associated with an increased the risk of all-causes of dementia. Late life depression increased the risk of vascular dementia more than it increased the risk of AD, but it was independently a risk factor for both AD and VaD in older adults (Diniz et al., 2013). In a Swedish longitudinal study of men conscripted for mandatory military service and followed for 32-42 years, depression together with alcohol intoxication and low cognitive function at baseline were the strongest independent risk factors for

development of early onset dementia (Nordstrom et al., 2013). All nine independent risk factors (alcohol intoxication, stroke, use of antipsychotic drugs, depression, father's dementia, drug intoxication other than alcohol, low cognitive function at baseline, high systolic blood pressure at baseline and low height) found in this study had an multiplicative effect and accounted for 68% of the cases of early onset dementia identified.

Reversible cognitive impairment in connection with depression late in life (often called pseudodementia) is also shown to be a strong predictor of later development of dementia (Alexopoulos et al., 1993, Saez-Fonseca et al., 2007). According to one study, many of these depressed patients maintained some form of cognitive impairment after remission of depression, and as many as 40% of these patients develop irreversible dementia within three years of follow up (Alexopoulos et al., 1993). Several authors have questioned whether depression could be the first sign of incipient dementia in addition of being a risk factor for later cognitive impairment or dementia, at least if the onset of depression is closer in time to the development of dementia (Saez-Fonseca et al., 2007, Barnes et al., 2012, da Silva et al., 2013). Depression in younger people with dementia is also often seen among people with a history of previous depression (Lyketsos and Olin, 2002, Rosness et al., 2010). Recently, Vilalta-Franch and colleagues found that late life depression with executive dysfunction increased the risk of development of dementia and AD independent of the severity of depression (Vilalta-Franch et al., 2013).

Previous depression and the type of dementia

There are some contradictive findings concerning the association between previous depression and the type of dementia, e.g., whether recurrent depression earlier in life is more associated with VaD than with AD (Kessing, 2012). Diniz reported a stronger association with depression and VaD than with AD in the meta-analysis (Diniz et al., 2013). Depression in mid-life and late-life are associated with an increased risk of both AD and VaD in one study. In a huge longitudinal study, the authors found that the risk of AD was doubled and the risk of VaD was tripled if the patient had one or more episodes of depression earlier in life (Barnes et al., 2012). The authors said recurrent depression late in life may reflect the development of cerebrovascular changes that may predispose for VaD.

Depression as a comorbid condition to dementia

The most frequent co-morbid psychiatric disorder in dementia is depression, with a prevalence rate at syndrome level of 50% and at disorder level of 25%, regardless of the

degree of dementia (Olin et al., 2002a, Lyketsos and Olin, 2002, Barca et al., 2010b). This is not only found in the Western world but also in low income countries and across different cultures (Shah et al., 2004, Starkstein et al., 2005b, Chahine et al., 2007). The prevalence of depression in dementia varies considerably in different studies and depends on the populations studied, measurement scales, and diagnostic criteria being used (Olin et al., 2002a). One reason for the discrepancy may be that the symptoms of depression are not always pronounced and symptoms of depression and dementia may overlap (Ballard et al., 1996, Starkstein et al., 2008), even though all authors do not agree that the symptoms of the two conditions overlap significantly (Engedal et al., 2011). During the course of dementia, more depressive symptoms are found among those with subcortical dementias such as VaD, Parkinson's disease, and Huntington's disease compared to those with cortical dementias (Barca et al., 2012). AD patients with subcortical pathology (white matter lesions) have more depressive symptoms than those without (Alexopoulos et al., 2005). Deep white matter lesions, often seen in patients with dementia, are associated with chronic depression.

Depression and the severity of dementia

It is hypothesized that depression in cases of mild dementia is caused by psychological factors such as the patient's insight into his or her functional decline, loss of memory function, and dysfunction in everyday activities, while depression in severely demented patients could be explained by structural changes of the brain. The high prevalence rate of depression in the late stage of the disease most probably indicates that biological factors or functional decline might be important as dementia progresses.

A few autopsy studies have shown that cell loss in dorsal raphe (serotonin) and locus coeruleus (noradrenalin) in AD patients were associated with chronic depression before death (Forstl et al., 1992). One post-mortem study showed that damages in amygdala of AD patients were associated with depression (Lopez et al., 2006). Another explanation for persistent depression in AD and dementia in general could be explained by cerebrovascular factors as described in this manuscript.

Newer studies have not confirmed that insight into having dementia is associated with an increased risk of depression (Lyketsos and Olin, 2002, Even and Weintraub, 2010). These studies have not found a correlation between depressive symptoms and awareness of cognitive deficits. Previously it was thought that depressive symptoms were more common in the early stages of dementia. This probably reflects the fact that diagnosing depression

becomes increasingly difficult as the level of cognitive impairment worsens (Olin et al., 2002a). No such association could be found in a systematic literature review done to gain more insight into the association between severity of AD and prevalence of co-morbid depression (Verkaik et al., 2007).

Symptoms

Depression in dementia presents itself in a heterogenetic way. Sadness is common in depression among patients with and without dementia. A study of depressed AD patients found that the same symptoms were also present in patients without dementia. Sadness, loss of interest, agitation, retardation, and loss of concentration were the most common symptoms (Engedal et al., 2011). Other studies also found that depressed patients with AD have similar depressive symptoms to those without dementia (Chemerinski et al., 2001, Starkstein et al., 2005b). Apathy is not necessarily a symptom of depression even though it may be a marker or prodromal stage of depression in dementia (Starkstein et al., 2005b). A longitudinal nursing home study showed that apathy and depression were distinct clinical entities (Selbaek et al., 2013a). Others found the same (Even and Weintraub, 2010). The severity of signs and symptoms of depression in dementia may be less pronounced than during a major depressive episode. Symptoms of depression in dementia can include anxiety, agitation, social isolation, withdrawal, loss of interest or irritability (Olin et al., 2002a, Barca et al., 2008), but these symptoms are also common symptoms of dementia. That may complicate both assessment and treatment of a patient. AD patients report diminished ability to concentrate, sleep disturbances, feelings of worthlessness or excessive guilt more often than depressed elderly without AD (Even and Weintraub, 2010).

Traditional and new provisional criteria

The symptoms of depression in dementia may be less intense than in patients without dementia, and recently there has been a discussion about the validity of the traditional diagnostic criteria (ICD-10 and DSM-IV) for depression in dementia. In 2002, a new set of diagnostic criteria for depression in subjects with dementia were proposed, called the Provisional Diagnostic Criteria for Depression of Alzheimer Disease (PDC-dAD) (Olin et al., 2002b). These new criteria were modified from the DSM-IV criteria for major depression. Instead of five or more symptoms, the patient must have three or more symptoms of depression to fulfill the criteria for major depression. The presence of irritability and social withdrawal were added as two new symptoms of depression in this special patient group. The symptom, loss of interest or pleasure, was revised so it reflects a less positive affect or

pleasure in the patients toward social contact and usual activities, and dismissed ability to concentrate was removed. See Table 6. According to the PDC-dAD, the symptoms must not be present nearly every day, but may have a fluctuating course. Suicidal thoughts and melancholic symptoms are less emphasized in PDC-dAD, and psychosocial factors may be of less importance. Using the PDC-dAD, more AD patients are considered depressed than with the criteria of DSM-IV and ICD-10 (Even and Weintraub, 2010, Engedal et al., 2011).

Table 6. Provisional diagnostic criteria for depression of Alzheimer Disease

A.	Three or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either 1) depressed mood or 2) decreased positive affect or pleasure.
	1) Clinically significant depressed mood (e.g. depressed, sad, hopeless, discouraged, tearful)
	2) Decreased positive affect of pleasure in response to social contacts or usual activities
	3) Social isolation or withdrawal
	4) Disruption of appetite
	5) Disruption to sleep
	6) Psychomotor changes (e.g. agitation or retardation)
	7) Irritability
	8) Fatigue or loss of energy
	9) Feelings of worthlessness, hopelessness or excessive or inappropriate guilt
	10) Recurrent thoughts of death, suicidal ideas, plan or attempt
B.	All criteria are met for Dementia of the Alzheimer type (DSM-IV-TR)
C.	The symptoms cause clinically significant distress or disruption in functioning
D.	The symptoms do not occur exclusively during the course of delirium
E.	The Symptoms are not due to the direct physiological effect of a substance (e.g. drug of abuse or a medication
F.	The symptoms are not better accounted for by other conditions such as major depressive disorders, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorder, or substance-related disorder.

Prognosis

The persistence rates of depression among cognitive impaired and demented patients living at home vary from 33% to 58% in different studies (Haupt et al., 2000, Garre-Olmo et al., 2003,

Steinberg et al., 2004). The different persistence rates may reflect variations in the groups of patients being examined and different diagnostic tools being used. In most studies a cutoff point on a depression scale is used to define depression and diagnoses are seldom made; this could be one factor that explains the differences in persistence rates. However, depressive symptoms vary during the course of dementia and they often become less severe with the progression of dementia (Aalten et al., 2005, Selbaek et al., 2013a). All these figures are unsecure because few long-term follow-up studies of depression in dementia have been published. Some studies report that the symptoms vary over time (Olin et al., 2002a) and persist in 30% to 40% of the patients (Lyketsos and Olin, 2002, Barca et al., 2010a, Bergh et al., 2011). In most studies, the follow up is too short to say anything for sure about the duration (months up to one year). In a one-year follow-up study among people in care facilities, more than 60% of depression had resolved during that year independently of pharmacological treatment. There is limited published data on the impact of depression on morbidity and mortality (Olin et al., 2002a), but studies found a higher mortality rate among patients with comorbid depression (Barca et al., 2010a). The risk of being admitted to institutional care seems to increase among patients with comorbid depression in dementia (Starkstein et al., 2008).

Many of the same vascular risk factors are seen in depression and dementia (Kivipelto et al., 2001, Almeida et al., 2007, Teper and O'Brien, 2008, Kivipelto and Solomon, 2008). It is possible that the same underlying condition may be responsible for both disorders. Therefore, lifestyle and pharmacological interventions may have considerable impact on reducing depression in dementia, or at least postponing the onset of dementia (Kivipelto and Solomon, 2008).

Possible interaction between MCI, AD and late life depression

Alzheimer's disease (AD) and depression in elderly subjects have many biological factors in common. AD and late life depression share the same vascular risk factors. Many of the same neurodegenerative changes (in the hippocampus and other parts of the brain) that are found in the brain in AD and other dementias are also seen in depression (Leonard, 2007).

Chronic inflammation is considered central in the pathogenesis of major depression. Results from studies indicate that inflammatory processes (cytokines) may play a pathogenic role in depressive disorders (Leonard, 2007). Tumor necrosis factor (TNF) α, interleukin (IL)-1 and -6 are examples of cytokines that are raised in depression and in the elderly. These cytokines

initiate different cascades such as an activation of the hypothalamic-pituitary-adrenal (HPA) axis with production of glucocorticoids. In addition, the production of neuroprotective substances is inhibited, which strengthens the cytokines' cytotoxic effect. Some studies have found a high correlation between the severity of depression and the levels of pro-inflammatory cytokines (Thomas et al., 2005, Caraci et al., 2010). A wide range of inflammatory markers, typically absent in the normal elderly population, have been found in AD. These markers often correspond to those found in major depression. Cytokines are found in the inflammatory processes located close to the amyloid plaques in AD. If we presume that the cytokines serve similar intercellular and intracellular signaling processes in microglia and astrocytes as they do in the periphery, chronic cytokine production might be cytotoxic and might stimulate the production of beta-amyloid. Therefore it is reasonable to believe that the two conditions can interact with each other. It is hypothesized that the progression from depression to dementia could result from the chronic inflammatory changes seen in depression. This may explain why chronic major depression is a frequent prelude to dementia in the elderly patient (Leonard, 2007). In addition, a post-mortem study observed more hippocampal plaques and tangles in patients with AD that had a lifetime history of depression than AD patients without depression (Rapp et al., 2008).

Also, ApoE e-4 carriers with AD showed a higher spontaneous production of IL-1beta, and a significant association was found between behavior in the patients with dementia and IL-6 production. A connection between inflammation and the effect of Apoe E-allele in the development and progression of AD might exist (Olgiati et al., 2010). Another follow-up study showed that ApoE e4 carriers with a diagnosis of MCI and co-morbid depression have a higher risk of developing Alzheimer's disease than MCI patients free of depression (Modrego and Ferrandez, 2004). Thus, it might be that treatment with anti-inflammatory agents could slow down the Alzheimer progress in some patients, especially in those with co-morbid depression. Randomized controlled trials have not shown any effects of such treatment, but these trials did not select patients with the double diagnosis of AD and depression and did not consider the effect of the ApoE genotype.

Treatment

The guidelines for treating depression in dementia are pretty much the same as for depression in old age without dementia. However, the documentation of the effect is much poorer (Lyketsos and Lee, 2004). Some psychological interventions have shown some effects. The challenge when comparing different studies is the heterogeneity in methods and interventions.

Often there is little evidence available for different psychosocial interventions, and the studies are also often small (Livingston et al., 2005). Few studies of acceptable quality were found in a systematic review of psychological intervention from 2013 (Regan and Varanelli, 2013). Patients with MCI and early stage dementia may benefit from tailored interventions such as problem solving and cognitive behavioral therapy. The evidence was best for studies with a problem solving approach (Regan and Varanelli, 2013). However, some of the effect found in these studies may be due to the positive effect achieved by taking part in a study rather than the intervention itself, called the Hawthorne effect. Psychosocial interventions should be tried in mild to moderate depression (Lyketsos and Lee, 2004), which is also the recommendation for the treatment of depression of mild degree in patients without dementia in Norway (Helsedirektoratet, 2009).

Antidepressants are considered safe for patients with depression and dementia, but may have severe side effects in some patients. Several randomized controlled trials (RCT) have been conducted to compare antidepressants and placebo. Most of them have included a low number of patients. The studies vary concerning the type of antidepressant medication, duration of study period, inclusion and exclusion criteria, type and severity of dementia and depression. A 2011 study by Banerjee et al. randomized 326 AD patients into three groups. Two groups received antidepressant and one group received a placebo. There was no difference between the three groups after 13 or 26 weeks (Banerjee et al., 2011). Most of the studies showed disappointing results. Three meta-analyses of good quality of pharmacological treatment for depression in dementia have been published. Two of them show weak evidence for the efficacy of antidepressant for depression in patients with dementia (Bains et al., 2002, Nelson and Devanand, 2011), while one is more positive (Thompson et al., 2007). However, some patients benefit from antidepressants so they should be considered in the moderate to severe depression group (Lyketsos and Lee, 2004, Bergh et al., 2012b).

Traditionally ECT is seldom used in depression among patients with dementia because of the presumed risk of delirium. Therefore, few studies considering the effect and safety are carried out. However, some studies have found ECT effective and well tolerated in geriatric depressed in-patients regardless of pre-existing cognitive impairment. The cognitive deficits were transient (Rao and Lyketsos, 2000, Hausner et al., 2011); therefore ECT should be considered in severe and refractory cases.

1.6 Assessment scales/screening instruments

A psychiatric assessment of every patient with dementia would be a good way to reveal psychiatric symptoms or depression at the disorder level. This is seldom possible because it is time- and resource-consuming in a busy clinical practice. Many different scales measuring depressive symptoms are in use. Some scales are based on information from the patients as other use information from a family caregiver or a nurse. Some scales are based on self-report (self-assessment) and others are observation scales (clinician-rated scales). Only a few scales are developed specifically to assess depression in dementia, and this may explain some of the variation in the prevalence rate of depression in dementia in different studies. There is also an ongoing discussion about the validity and reliability of self-report scales, because a person with dementia could have little insight into his or her own situation and therefore underreport symptoms of depression and cognitive impairment (Lyketsos and Lee, 2004). Evaluation scales are nevertheless useful in screening patients for depression, determining the severity of depressive symptoms and quantifying changes of depressive symptoms after specific treatment (Starkstein et al., 2008). Thus, it may be practical to use standardized scales for the assessment and screening of depressive symptoms.

There are many challenges using depression scales on patients with dementia. The symptoms of depression are not always pronounced and some of the symptoms of depression and dementia may overlap (Ballard et al., 1996). However, this issue is open for discussion, because some researchers in the field would claim that depressed people with dementia have the typical symptoms of depression such as sadness, anxiety and loss of self-esteem (Zubenko et al., 2003, Barca et al., 2008, Engedal et al., 2011). Patients with dementia report their depressive symptoms less than caregivers and clinicians' appraisal (Chemerinski et al., 2001). On the other hand, patients with dementia often do not appear depressed during a consultation with a clinician, but family caregivers can report depressive symptoms in these same patients (Lyketsos and Lee, 2004). Also, depressed family caregivers may overestimate depression in the patients and family and professional caregivers may misconceive apathy as depression.

Discrepancies between the patient and proxy may not be a sign of reduced awareness of deficit in the patient (Snow et al., 2005). It seems that in the earliest stages of dementia the patients have at least some insight into their condition and can express their feelings (Beattie et al., 2004).

The next section will present some scales that are used rate depression in dementia.

Geriatric Depression Scale (GDS) (Yesavage et al., 1982)

The Geriatric Depression Scale is a self-assessment scale with 30 items. It is also used as a semi-structured interview with patients. A short version with 15 items and a very short version with 5 items have been developed. A score of 11 and above on the 30-item version indicates depression. The GDS is not developed for use in dementia, and when compared with the Cornell Scale for Depression in Dementia (CSDD), it is less suitable than the CSDD among those with more severe cognitive impairment (Burke et al., 1989, Lam et al., 2004, Korner et al., 2006). Furthermore, it depends more on the severity of dementia than the CSDD (Muller-Thomsen et al., 2005). However, in milder cases of cognitive impairment, it is valid as a screening tool (Debruyne et al., 2009).

Beck Depression Inventory (BDI) (Beck et al., 1961)

The Beck Depression Inventory is a self-report scale that was developed in 1961. It has been revised twice since then in 1978 and 1996. The last revision was extensive, and harmonized the items with the criteria of the DSM-IV. The BDI was not made for use in the elderly especially, but for use in the general population. A study performed among elderly found that older people tend to get higher scores on the somatic and performance subscales than younger people. No difference between younger and older people was found in use of the cognitive affective subscale (Trentini et al., 2005). The BDI is not satisfactory in measuring depression in AD, because it tends to underdiagnose depression (Wagle et al., 2000).

Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960)

The Hamilton Depression Scale (HDS) was developed in 1960 as a clinician rating scale with 21 items. A score of 7 or higher indicates the presence of depressive symptoms. A 17-item version also exists. The HDS was not particularly designed for use in the elderly or among persons with dementia, but it is a very common scale, especially in American studies. In the U.S., it is often used as the gold standard in depression treatment studies among patients with severe or psychotic depression, because it measures the intensity of the symptoms. It includes questions about somatic symptoms, and is therefore increasingly replaced by the MADRS in clinical trials, including elderly patients with co-morbid physical disorders. The HDS has been shown to be less sensitive to changes after treatment in AD (Lyketsos and Lee, 2004).

Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983)

The Hospital Anxiety and Depression Scale (HADS) is a 14-items self-assessment scale designed to identify emotional distress in patients in non-psychiatric hospital units. The questionnaire includes seven items that measure anxiety and seven items that measure depression. It is formulated in a language easy to understand for the patients, avoiding somatic symptoms of depression and anxiety. Symptoms of more severe psychopathology are not included in order to increase its acceptability. In the depression subscale (HADS-D), five of the items focus on loss of pleasure and reduced pleasure response (anhedonia), which are nonspecific indicators of depressed mood. A sum score above 8 on each subscale indicates a disorder (anxiety and/or depression). In a review, the scale was found to be both reliable and valid as a screening tool for assessing anxiety and depression in medical in-patients (Helvik et al., 2011). However, later studies found a much lower performance in older populations, both among patients with and without dementia (Samaras et al., 2013). HADS may not be as suitable as other depression scales among elderly in-patients.

The Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988a)

The Cornell Scale for Depression in Dementia (CSDD) was developed by Alexopolous and colleagues in 1988, and specifically designed to assess depressive symptoms in an elderly population with dementia living in institutions. However, in the original study, the CSDD was also validated among elderly persons without dementia (Alexopoulos et al., 1988b). It is a caregiver-based scale, but additional information from the patient should be included. The normal procedure is that a clinician fill in the scale based on an interview with a caregiver, either a family member or a professional caregiver. Thereafter, the clinicians should observe or talk with the patients and make corrections if necessary.

The CSDD is a 19-item scale in which every item can be scored between 0 and 2 (absent, mild/intermittent and severe) with a maximum score of 38. In the original publication, a score between 8 and 12 was suggested for mild depression in people with dementia and a score more than 12 for moderate or severe depression. According to Alexopolous et al., the scale is divided into five paragraphs: A. mood related signs, B. behavioral disturbances, C. physical signs, D. cyclic functions and E. ideational disturbance. However, later factor analyses of the scale have not found that the symptoms cluster into these five subgroups (Harwood et al., 1998, Barca et al., 2008). Patients with severe physical complaints will have a falsely higher score because of items concerning physical signs. In advanced stages of dementia it may be difficult to assess the items “ideational disturbances”.

The Montgomery-Aasberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979)

The MADRS was developed for use in cognitively intact patients, but is often used in mildly cognitively impaired or even in mildly demented people. It was designed to measure effects after treatment for depression, but is often also used as a screening tool. It is an observer-based scale that includes ten items: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. The symptoms of concentration difficulties and lassitude may overlap with symptoms of dementia; otherwise there are no items measuring somatic symptoms. Each item can be scored between 0 and 6, with a maximum score of 60. Traditionally a score more than 20 is considered a cut off for mild depression and a cut off of 30 for severe depression. Among the elderly in Norway, a cut off of 15 has normally been used. However a recent Norwegian study among elderly non-demented patients showed that the optimal cut off score for separating depressed elderly for non-depressed was 16/17 (Engedal et al., 2012b). In this validation study, a DSM-IV diagnosis of depression was used as the gold standard. The MADRS was suitable as a screening instrument to separate depressed from non-depressed patients. Few studies have examined the validity of the MADRS among elderly patients. The MADRS was validated in some studies with patients with dementia, and it has been found suitable at least in the less severe cases of dementia but with less discriminatory power than in patients without dementia (Leontjevas et al., 2009, Knapskog et al., 2011, Portugal et al., 2012, Leontjevas et al., 2012).

1.7 Psychometric characteristics of tests and evaluation scales

Diagnostic tests and evaluation scales are predictors and not explainers of diagnoses. They are influenced by many factors, and maybe with the exception of biopsies, few tests and scales will change the decision made by the clinical impression in a conclusive way. However, they can contribute to the probability that a disorder is present. The setting where the test and scales are carried out will influence the performance and result. This is especially true for the use of neuropsychological tests and evaluation scales.

Validity

Validity is the degree to which an instrument truly measures what it is supposed to measure. Many aspects must be taken into account when validating a test or a scale. A test should be validated against a gold standard or an acceptable reference standard such as a set of criteria for a diagnosis (DSM or ICD), for example. This comparison should be independent and blind. Both the diagnostic test/evaluation scale and the reference standard should be interpreted independently from each other; otherwise a positive diagnostic test tend to over-interpret the reference test and a negative diagnostic test tend to under-interpret the reference test. The reference standard should be applied to all patients regardless of the result of the diagnostic test; otherwise the result of the diagnostic test could influence the decision to undergo confirmation by the reference test (verification bias). It is also important to validate a test among the same type of patients to which it should be applied. Patients with and without the specific disease should be included in the validation study, and both mild and more severe cases of the disease should be included (broad spectrum of patients). The patients should be recruited randomly or consecutively, because if there is any selection the test may not perform well in another group of patients. After an initial study, the test should be validated in a second, independent group of patients. In addition, all participants, both diseased and healthy persons, or contrast group (a contrast group could consists of people seeking health service because of complaints, but that are found to be healthy after assessment) should be examined in the same way (Sackett et al., 2000, Qizilbash, 2002).

The confidence level in a diagnosis is based on clinical expertise, experience and a finding that is called the pretest probability. The pretest probability is equal to the prevalence of the disease in the population studied before clinical assessment has been performed. The pretest probability has the greatest influence dementia diagnosis in people with cognitive impairment, for example. If it is unlikely that the person has dementia, a test is unlikely to change this pretest probability, and consequently the pretest probability will be higher in a specialist center than in primary care (Qizilbash, 2002). For example, the prevalence of dementia is below 1% in people younger than 65 years of age. If people of this age visit his/her doctor and do not complain about any decline in cognition, the pretest probability is also below 1%. In contrast, a person aged 80 years will have a pretest probability of dementia of about 20% when he/she does not have any complaints about reduced cognition. If a person of the same age complains about a memory problem and this is confirmed by his or her cohabitant, the pretest probability will increase above 20% and could be as high as 40%.

The probability of having a positive test result in individuals with a disease is called sensitivity, and the probability of having a negative (normal) test result if you do not have the disease is called specificity. Knowing a test's sensitivity and specificity, it is possible to calculate positive and negative likelihood ratios (LR+ and LR-). Likelihood ratios indicate how much the risk for a disease changes based on a positive or negative test result, because it summarizes the discriminatory power of a diagnostic test. LR+ is defined as the probability of having a positive test if the disease is present divided with the probability of a positive test in a person without the disease (sensitivity/(1-specificity)). It indicates how much the odds of a disease increase when a test is positive. The LR- is defined as the probability of having a negative test if the disease is present divided by the probability of a negative result in a person without the disease (1-sensitivity)/specificity). It tells how much the odds of disease decrease when a test is negative. The LR indicates the degree by which the pretest probability will increase or decrease. If the LR is 1, the post-test probability of a disease is the same as the pretest probability. If it is greater than 1, the probability that the disease is present increases. Values between 2 and 5 have a small impact on the pretest probability, values between 5 and 10 have a modest impact and values above 10 have a major impact (Qizilbash, 2002).

The post-test probability is calculated by combining the pretest probability of a disease in a group of patients and the likelihood ratio for a positive test result. See Figure 4. However, the prevalence of the disease (pretest probability) influences the post-test probability more than sensitivity and specificity. The limitations of the calculation of sensitivity and specificity are that they cannot be used directly to calculate post-test probabilities. They require the results to be dichotomous, i.e., yes/no or present/absent. When calculating cut-off points, the numerical variables are transferred to binary classifications by constructing receiver-operating characteristic (ROC) curves. In the ROC curve, the vertical axis represents the true positive rate (sensitivity) for different cut-off points, and the horizontal axis represents the false positive rate (1-specificity) for the same cut-off points. The value of each cut-off point is generated and expressed as a line. Therefore it is possible to compare the values of different tests by assessing the area under each curve. The closer both sensitivity and specificity are to 100%, the better is the discrimination power of the test (Qizilbash, 2002).

Another way of expressing validity is to use the concept accuracy. Accuracy is the sum of all individuals correctly diagnosed as positive and negative (both). Accuracy gives information about how well the test divides the patients into groups depending on whether they have the disorder or not, but gives no information about the false positive or false negative rates.

Predictive values describe the probability that the test result is correct. Positive predictive value (PPV) is defined as the probability of being ill when the test is positive, and negative predictive value (NPV) is the probability of not having the disease when the test is negative. They both depend on the prevalence of the disease in the population (whereas LR is not), and the sensitivity and specificity of the diagnostic test used. See Tables 7 and 8.

Table 7. The relationship between a test and a disease: - A 2 x 2 table of the possible results (a-d) from comparing a diagnostic test to be validated and a reference standard

	Reference standard		
Test	Disease present	Disease absent	Sum
Test positive	a (true positive)	b (false positive)	a + b
Test negative	c (false negative)	d (true negative)	c + d
Totals	a + c	b + d	N = a + b + c + d

Table 8. Properties of a diagnostic test

Sensitivity: a/(a+c)
Specificity: d/(b+d)
Prevalence of the diagnosis in the study population: (a+c) / (a+b+c+d)
Positive predictive value (PPV): a / (a+b)
Negative predictive value (NPV): d / (c+d)
Accuracy: (a+d) / (a+b+c+d)
Positive likelihood ratio (LR+): sensitivity / (1-specificity)
Negative likelihood ratio (LR-): (1- sensitivity) / specificity

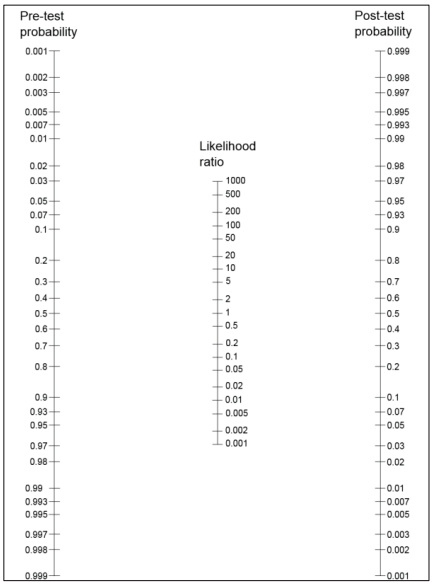

Figure 4. A nomogram for applying likelihood ratios. Adapted from Fagan, 1975

Reliability

Reliability is a term used to describe how repeatable a measurement is, i.e., if it is possible to repeat the result of the measurement studies conducted on several occasions by the same rater or by several raters. It describes how consistent the test result is, but not whether the instrument measures what it is meant to measure (that is validity). In other words, reliability is used to describe to which degree the measurement is free of measurement error, and whether the patients can be distinguished from each other despite systematic or random measurement errors. Reliability can be divided into: 1) inter-rater reliability: whether two raters get the same result; 2) intra-rater reliability: whether the same rater gets the same result if the measurement is repeated; and 3) test-retest reliability: whether the result remains the same from day to day, provided the patient has not changed (de Vet et al., 2011).

Commonly used reliability parameters are the intraclass correlation coefficient (ICC) and Cohen's kappa.

Intraclass correlation coefficient (ICC)

ICC is a parameter for reliability for continuous variables. There are various ICC formulas, but they all consist of a ratio of variances with values that range between 0 and 1. ICC is sample-dependent. A value of 1 means the error variance is negligible compared to the

variance of the patients. If the ICC is 0, the error variance is extremely large compared to the patient variance. This may occur in very homogeneous samples of patients. Patients in a heterogeneous population are much easier to distinguish than patients that are very similar.

Cohen's kappa

Cohen's kappa (κ) is a parameter of reliability for categorical variables organized either as a nominal scale (unweighted kappa) or an ordinal scale (weighted kappa). Cohen's kappa adjusts for the agreement that is expected by change (expected agreement). K values range between -1 and 1, where 0 is no more agreement than can be expected by change and -1 means there is a reversed scaling by one of the raters. When κ is 1 there is a complete agreement between two readings made by two different observers. Values of 0.77 or greater are considered excellent.

Internal consistency is also considered an aspect of reliability. Internal consistency is an assessment of the consistency of the different items within a scale.

Cronbach's alpha

Cronbach's alpha is a commonly used reliability parameter that measures the internal consistency of a scale. It increases when the correlation between the items on the scale increase. It represents a mean value of the correlations between the different items or groups of items (s 82 de Vet). The values should be between 0.7 and 0.9. Values higher than 0.9 indicate that some items can be deleted. By limiting the number of items, the test becomes more efficient. If Cronbach's alpha is too low, the value will increase by formulating new items. Cronbach's alpha reflects the variance of the items within the scale; it does not assess whether the model is reflective or informative. However, internal consistency is not a measure of unidimensionality (i.e., factor analyses) of the scale, and a high internal consistency does not imply the test-retest reliability is also high. It cannot replace test-retest reliability (de Vet et al., 2011).

2 The present study

2.1 Aims

The overall aims of this study were to explore the patterns and prevalence of depressive symptoms as reported by patients and caregivers among patients referred to memory clinics and (geriatric and old-age psychiatry) outpatient clinics for dementia assessment, and to validate depression scales for the detection of a depressive disorder. Four sub-studies were conducted.

The aims of the sub-studies were:

- To validate the CSDD and the MADRS among memory clinic patients in Norway;
- To explore the prevalence of depression among patients referred to a memory clinic or an outpatient clinic for dementia assessment as measured by the CSDD and to investigate which factors were associated with depression;
- To compare the results of the CSDD by interviewing a caregiver and the results of the MADRS by interviewing the patients in a memory clinic population;
- To explore cross-cultural differences in scores on the CSDD and the MADRS among elderly outpatients in Brazil and Norway.

2.2 Study design

For all four sub-studies, a cross-sectional design was applied. The data were obtained at the first visit to the outpatient clinics for assessment of cognitive impairment for all patients, except for 20 patients at Innlandet Hospital Trust (SI) who were included in sub-study I. These 20 participants were included when they came for follow-up.

For the validity study (sub-study I), we used the criteria described by Sackett el al. for "critical appraisal" of diagnostic tests (Sackett et al., 2000). According to Sackett, a test has to have the ability to correctly distinguish patients who have the disease from those who do not

have the disease. To be valid, a test has to be compared independently and "blind" with a reference ("gold") standard of diagnosis. The reference standard has to be used regardless of the test result. It is also important that the test is evaluated in the group of patients to whom it is normally applied and to know if the test has the ability to accurately distinguish patients who have a disease from those who do not. In this regard, it is important to note that healthy controls are not an appropriate reference group.

For the prevalence of depression study (sub-study II), data from a register of patients referred to and examined at collaborating clinics in the southern, eastern, and western parts of Norway were used. In this register, the patients included were assessed in the same way, using a standardized protocol. At the two memory clinics that include most patients in the register, Oslo University Hospital (OUS), Ullevaal, and Innlandet Hospital Trust (SI), 90 percent of the patients coming for dementia assessment give consent that the data of the assessment can be included in the register and used for research. For the other clinics, we do not have the exact rate of participation.

For the comparison of the CSDD and the MADRS (sub-study III), data from the same register were used, but data were also included from people recruited before the memory clinic register was established. In the period from 1990 to 2008, all patients referred to the memory clinic at Oslo University Hospital, Ullevaal, were included in a local register at the hospital.

For the cross-cultural comparison (sub-study IV), the same design as for the validity study (sub-study I) was applied. The comparison was planned ahead of the study, and the researchers working in Rio de Janeiro and Oslo met in Rio before the start of the study and twice during the study (in Oslo and Rio, respectively) to ensure that a common design and procedure for data collection, including how to diagnose depression at the disorder level, were followed.

2.3 The subjects

The majority of the patients were recruited from Oslo University Hospital (OUS), Ullevaal, and Innlandet Hospital Trust (SI) in Norway. For the validity study (I) and the cross-cultural study (IV), the patients were recruited in an unselected manner when they came for examination to the two hospitals on workdays when a psychiatrist was present. For the correlation study (III), we used data obtained from two registers of patients. The first register,

the local register, included only patients who were referred to OUS, Ullevaal, in the period before 2009. The other memory clinic register, today acknowledged as a National Dementia register, included patients referred to and examined at collaborating clinics in southern, eastern, and western parts of Norway. This national register was established in 2009 and will continue to include patients until 2029 or until 5000 patients are included. In the prevalence study (II), we used information from the national dementia register. Data were obtained from patients in twelve clinics. Table 9 shows the number of patients, their ages, and genders, and the primary diagnoses of the patients who were included in the four sub-studies.

Table 9.The table shows the number and main characteristics of the patients included in sub-studies I to IV

	Validity study (I)	Prevalence study (II)	Correlation study (III)	Cross-cultural study (IV)
Number of patients	125	1470	520	211
Site of inclusion				
Oslo University Hospital	97	510	361	125
Innlandet Hospital Trust (SI)	28	298	159	
Other outpatient clinics		662		
Rio de Janeiro				86
Age (SD)	67.4 (9.2)	73.3 (11.0)	69.3 (10.9)	70.2 (9.2)
Women (%)	61 (48.8)	804 (54.7)	293 (56.3)	124 (58.8)
SCI, n (%)	29 (23.2)	203 (13.8)	110 (21.2)	38 (18.0)
MCI, n (%)	41 (32.8)	517 (35.2)	169 (32.5)	57 (26.9)
Dementia, n (%)	55 (44.0)	750 (51.0)	241 (46.3)	116 (55.0)

SCI = Subjective cognitive impairment; MCI = Mild cognitive impairment

2.4 Methods

Dementia diagnoses

All the patients were examined by a physician in a standardized and comprehensive manner according to a common research protocol (Braekhus et al., 2011) (see figure 5). The patients underwent a neuropsychological examination including a battery of neuropsychological tests.

A physical examination was performed, blood samples were collected, and different assessment scales were completed during interviews with both the patients and their caregivers. Each patient had a CT or an MRI brain scan, and some also had a SPECT. Additionally, some patients had a spinal fluid examination for measurement of beta-amyloid and tau proteins.

In Norway, we used the ICD-10 criteria for dementia diagnosis, and in Brazil, the DSM-IV-TR was used. To evaluate the severity of dementia, the Clinical Dementia Rating Scale (CDR) was applied (Hughes et al., 1982).

In Norway, we used the ICD-10 for research, and in Brazil, we used the DSM-IV-TR criteria to diagnose Alzheimer's disease, vascular dementia, and dementia related to Parkinson's disease. For frontotemporal dementia, the Manchester-Lund criteria (Neary et al., 1998) were used, and for Lewy Body dementia, the criteria according to McKeith and colleagues (McKeith et al., 2005) were used.

Mild cognitive impairment (MCI) was diagnosed using the Winblad criteria (Winblad et al., 2004). In those cases for which neither the criteria for dementia nor MCI were met, the term "subjective cognitive impairment" was used for patients referred to a memory clinic for "dementia assessment."

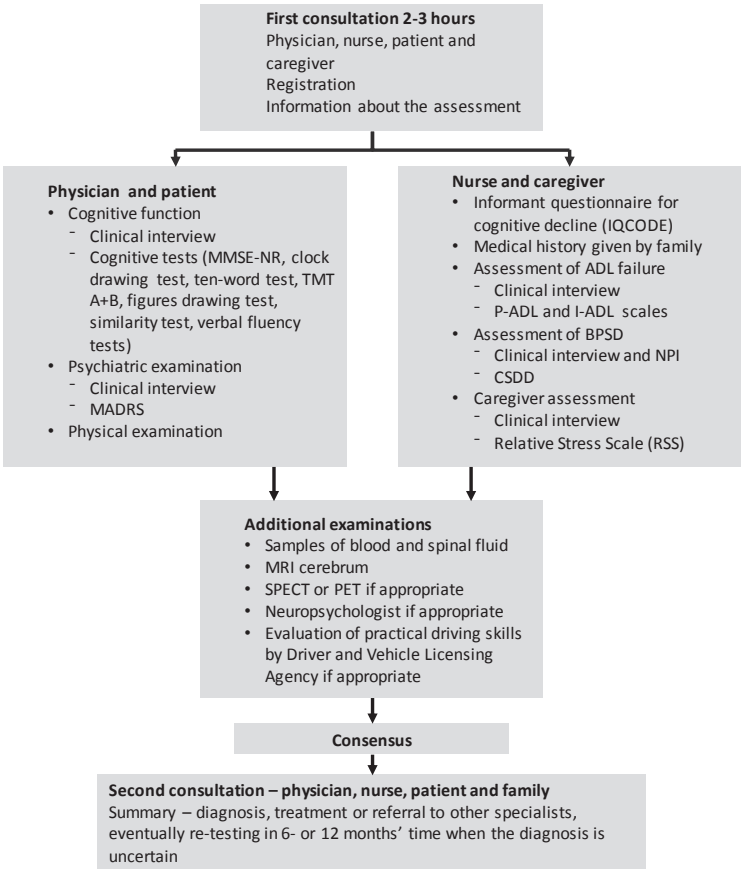

Figure 5. Procedure for the dementia assessment at the Memory Clinics. Adjusted from Braekhus et al., 2011

MMSE-NR = Norwegian revision of Mini Mental Status Examination. TMT A and B = Trail Making Test A and B, MADRS = Montgomery-Aasberg Depression Rating Scale, IQCODE = Informant Questionnaire for Cognitive Decline, ADL = Activities of Daily Living, P-ADL = Personal ADL, I-ADL = Instrumental ADL, BPSD = Behavioral and psychological symptoms of dementia, NPI = Neuropsychiatric interview guide

Depression diagnoses

Depressive symptoms were evaluated using the CSDD and the MADRS. The CSDD was completed by a nurse based on an interview with a caregiver, and the MADRS was completed by the physician based on an interview with and observation of the patient. The scales were completed "blind" to each other on the same day, i.e., the nurse and the physician did not have access to each other's interviews. This procedure was the same for all four sub-studies. For more details about the scales, see the section "assessment scales." In the validity study (I), a

diagnosis of depression was made using both the ICD-10 criteria for research and the DSM-IV criteria. The diagnosis of depression was considered the "reference standard" in the study. Both criteria were applied because we expected the prevalence of depression to be much higher using the ICD-10 criteria, as these criteria include patients with depression of a milder degree than the DSM-IV criteria for major depression. In this way, it was possible to compare the two sets of criteria. Three geriatric psychiatrists who were not involved in the assessment at the memory clinics evaluated the patients in Norway. They had access to the information in the records, except for the scores on the MADRS and the CSDD ratings (blinded to the results for the scales). The psychiatrists interviewed the patients and used a template with a list of all the symptoms of depression with regard to the ICD-10 (F32: mild, moderate, or severe depression) and to the major depression criteria of the DSM-IV in the interview session. At Oslo University Hospital, the interviews took place the same day as the data for the MADRS interview and the CSDD were collected, whereas the psychiatric interviews at Innlandet Hospital took place within a week after the patients had been assessed with the two scales. The duration of each psychiatric interview was 20 to 30 minutes, depending on the symptom load of each patient. One of the psychiatrists in Norway interviewed 68% of the patients. The three psychiatrists discussed the diagnostic procedures and the diagnoses with each other during the study to ensure the quality of each diagnosis, but no reliability study was performed. The same procedure was followed in the outpatient clinic in Rio de Janeiro, making the comparison possible (sub-study IV).

Other assessment scales

In the cross-cultural comparison (IV), the entire assessment of the patients was not identical. Different scales were used in the two countries in order to measure caregiver burden and functional status. In Brazil, the Zarit Burden interview (Zarit et al., 1980) and Pfeffer Functional Activities Questionnaire (Pfeffer et al., 1982) were applied. In Norway, the Relative Stress Scale (Greene et al., 1982) and the Lawton Instrumental Activities of Daily Living Scale (Lawton and Brody, 1969) were used.

2.5 Statistics

The statistics were performed using SPSS version 16 (sub-study I) and IBM SPSS version 19 (sub-studies II, III, and IV). Descriptive analyses were carried out for all sub-studies. Table 10 shows the various statistical methods that were applied to the four sub-studies.

Many of the variables did not show a normal distribution, which is an assumption for the use of parametric tests. Non-parametric tests do not require normal distribution and make no assumptions about the underlying population distribution. In this thesis, analyses were performed using the following non-parametric tests: Spearman's rho correlation, Chi square test, and Mann-Whitney U test.

Spearman's rho. Correlation is a way to describe the strength and direction of the linear relationship between two variables. Spearman's rho may be used when the variables are ordinal, interval, or ratios. The variables are converted to ranks before correlation analyses are performed. The correlation coefficient can range from -1.0 to 1.0. Values up to 0.29 are considered small; values between 0.3 and 0.49 are considered medium; and values between 0.5 and 1.0 are considered to indicate high correlation.

Chi square test. The relationship between two categorical variables is explored by the Chi square test. It explores whether the frequency of a variable is the same in different groups. Each variable may have two or more categories. In the prevalence study (II), the differences in prevalence rates were explored, using three different cut-off points for the CSDD (5/6, 7/8, and 12/13) among patients with various characteristics such as gender, age, diagnoses, and ADL impairment.

Mann-Whitney U test. This is the non-parametric alternative to the t-test, requiring two independent groups with continuous variables. Instead of comparing means, the Mann-Whitney U test compares medians. The scores on the continuous variables are converted to ranks that are compared.

Principal component analysis (PCA). PCA is a method of reducing a dataset. The original variables are decomposed into a set of factors. The loadings of the variables in each factor give information about the relative contribution that a variable gives to a factor. To make the interpretation of the analysis easier, the factors are "rotated." An orthogonal rotation method is used if the underlying factors are assumed to be independent, and it is easier to interpret

than the oblique rotation, where the underlying factors are assumed to be related or correlated to each other. This method is more difficult to interpret. Only factors with an eigenvalue of 1.0 or more are retained for further investigation (Kaiser's criterion). In the correlation study (III), PCAs were performed with varimax (orthogonal) rotation. Factor loadings ≥ 0.4 were considered significant and included.

Multiple linear regression analysis. This analysis is based on correlation and explores the relationship between one dependent continuous variable and a number of independent variables. With the standard method, all independent variables are entered into the analysis simultaneously. When a hierarchical method is chosen (sequential regression), the independent variables are entered in a specific order. Using the forward selection method, one new variable at a time is added, starting with the variable with the best correlation with the dependent variable. With backward deletion, the variables are removed one at a time. In the cross-cultural study (IV), simple and multiple linear regression analyses with log 10 CSDD and log 10 MADRS as dependent variables were performed. Transformation of the CSDD and MADRS scores was performed because they did not show a normal distribution. Age and gender together with all variables with p values < 0.2 in the unadjusted (simple) analyses were included in the adjusted (multiple) analyses. Adjusted analyses were performed using both standard and stepwise (enter and backward) methods. The results were the same.

Logistic regression analysis. In this analysis, the dependent variable is categorical, but the independent variables may be categorical, continuous, or a mix of both in the same model. It predicts categorical outcomes with two or more categories. In the correlation study (III), dichotomized CSDD scores were dependent variables. Variables that were associated with depression at p level <0.2 in the unadjusted analyses were included as independent variables in addition to age and gender. The independent variables were dichotomized or dummy dichotomized. Both standard and stepwise (backward and enter) methods were used, giving the same results.

As shown in Table 10, sensitivity, specificity, accuracy, likelihood ratios, and ROC analyses were also performed. These methods are described in chapter 1.7, Psychometric characteristics of tests and evaluation scales.

Table 10. Statistical methods used in the four sub-studies

Sub-study	Statistical methods
Validity study (I)	Receiver operation characteristics (ROC analyses) with area under the curve (AUC), accuracy, sensitivity, specificity, and likelihood ratios for positive and negative tests
Prevalence study (II)	Chi square analyses, correlation, and logistic regression analyses
Correlation study (III)	Correlation and principal component analyses
Cross-cultural study (IV)	Correlation and multiple linear regression analyses

2.6 Ethical considerations

The patients and their family caregivers gave their informed consent in writing. The studies were all approved by the Regional Ethics Committee for medical research in Southeast Norway and by the Data Inspectorate at Oslo University Hospital, Ullevaal.

When conducting research including patients with impaired cognition, it is of the utmost importance to judge their capacity to understand what they have given their consent to. As can be seen from the four papers, about half of the included patients did not have dementia, but had instead either MCI or SCI. Such patients will normally understand any information about a study. For those patients with a diagnosis of dementia, the majority had a mild degree of dementia, which also indicates that they have the capacity to understand. When in doubt, the issue was discussed with the patient's caregiver.

2.7 Results from the papers – the abstracts and additional information

The validity study (Paper I)

***Background**:* The aim of the study was to compare the validity of the Cornell Scale for Depression in Dementia (CSDD) and the Montgomery-Aasberg Depression Rating Scale (MADRS) among memory clinic patients.
Methods: The scales were independently completed for 125 patients. The diagnosis of depression was made by psychiatrists blinded to the depression scores.
Results: The mean score of the Mini-Mental State Examination was 25.5 (SD: 4.6), of the CSDD 6.8 (SD: 4.9), and of the MADRS 8.5 (SD: 6.8). In receiver operation characteristics (ROC) analyses, the AUC for the CSDD was 0.73 (95% CI: 0.63–0.82) using the ICD-10 criteria for depression, and 0.68 (95% CI: 0.57–0.79) using the DSM-IV criteria. The AUC was 0.88 (95% CI: 0.81–0.95) for the MADRS using the ICD-10 criteria, and 0.84 (95% CI: 0.76–0.92) using the DSM-IV criteria.
Conclusion: Both scales are suitable as screening tools. According to the ROC analyses, the MADRS seems better at distinguishing depressed from non-depressed patients.

<u>Additional results of sub-study I</u>
In this study, 41% of the patients met the ICD-10 criteria for depression; 65% of those patients had a mild degree of depression; 25% had a moderate degree; and 10% had a severe degree of depression. Using the DSM-IV criteria, 27% had a major depressive disorder. The cut-off with the best accuracy and with a balanced sensitivity and specificity for the CSDD was 5/6, and for the MADRS, the best cut-off point was 6/7, independent of which diagnostic criteria were used.

The mean Cornell score was 5.2 (SD: 3.7) in the group without depression and 9.3 (SD: 5.5) in the group with depression according to the ICD-10 criteria, and the mean MADRS score was 5.3 (SD: 5.2) for non-depressed subjects and 13.3 (SD: 5.9) for depressed subjects.

Approximately 54% of the patients had a CSDD score of 6 and above, indicating depression, and 52% had a MADRS score of 7 and above. Using the best cut-off score of the two scales, therefore, gave a higher prevalence rate of depression as compared to the psychiatric

diagnosis according to ICD-10 (41%). The correlation between the two scales was 0.43 for the whole group, 0.48 for the patients with dementia, and 0.44 for those without dementia.

The prevalence study (paper II)

Objectives: Depression in dementia is common, but the prevalence rates differ according to the populations studied and which diagnostic tools are being used. The aim of this study is to explore the prevalence of depression among patients referred to a memory clinic or an outpatient clinic as measured by the Cornell Scale of Depression in dementia (CSDD) and to investigate which factors are associated with depression.

Method: The CSDD was completed for 1470 patients on their first visit to a memory clinic or an outpatient clinic. The prevalence of depression using three different cut-off points was calculated. Logistic regression and correlation analyses were performed.

Results: Half of the patients had dementia. The mean CSDD was 6.7 (SD: 5.3) for the whole group, and 50.2% had a score above 5, whereas 37.5% had depression defined as a CSDD score above 7, and 14.1% had a score above 12. The mean scores were higher among those with dementia other than Alzheimer's disease, those with previous depression, and those with greater impairment in the activities of daily living (ADL). In the logistic regression analyses, younger age, ADL dysfunction, and previous depression were significantly associated with higher CSDD scores.

Conclusion: We found that depressive symptoms are common among patients referred for a dementia assessment in specialist health care. The strongest factors associated with depressive symptoms were younger age, ADL impairment, and previous depression.

Additional results of sub-study II

In this study, we included patients from 12 different outpatient clinics. Only two of them are identified as memory clinics (OUS and SI); the others are geriatric or old-age psychiatric outpatient clinics that also assess patients with diseases other than dementia and MCI. These outpatient clinics differed from the memory clinics in regard to demographic characteristics. In Table 11, we have compared the main characteristics of the patients from OUS and SI (n=808) with the patients from the remaining clinics (n=662). As can be seen, the patients of the two memory clinics (OUS and SI) are younger, fewer are women, and more are married; in addition, they have better functioning in terms of activities of daily living. The occurrence of comorbidities is also different, with less cardiovascular disorders among patients of the two memory clinics, which also leads to fewer patients with vascular dementia. While fewer of the

patients at OUS and SI have dementia, more have previous incidences of depression. Despite these differences, the mean score on CSDD was the same in both groups of patients. Including all patients, 50% had a CSDD score higher than 5.

Table 11. Patients' differences between the two groups of clinics

	Number or mean value	% or SD	OUS + SI (n=808)	The other clinics (662)	P value
Patient characteristics					
Mean age (n=1461)	72.5	10.8	68.6 (10.8)	77.3 (8.7)	<0.001[c]
Females	804	55.0	406 (50.5)	398 (60.5)	<0.001[a]
Married	935	63.6	576 (71.3)	359 (54.2)	<0.001[a]
Education (n=1380)	11.2	3.7	11.9 (3.9)	10.2 (3.2)	<0.001[c]
I-ADL (n=1398) (8-32)	13.5	5.3	12.1 (4.5)	15.2 (5.7)	<0.001[b]
P-ADL (n=1380) (6-30)	7.6	2.6	7.0 (2.1)	8.4 (3.1)	<0.001[b]
Comorbidity	1160	78.9	654 (80.9)	556 (84.0)	0.26[a]
Cerebrovascular diseases	343	23.3	168 (20.8)	175 (26.4)	0.07
Neurological diseases	290	19.7	195 (24.1)	96 (14.5)	<0.001
Cardiovascular diseases	792	53.9	389 (48.1)	403 (60.9)	0.001
Endocrine diseases	523	35.6	297 (36.8)	226 (34.1)	0.21
Cognition and dementia					
MMSE score (n=1450)	23.8	4.7	24.9 (4.1)	22.4 (4.9)	<0.001[b]
CDT score (n=1419)	3.5	1.6	3.7 (1.5)	3.2 (1.6)	< 0.001[b]
Diagnoses (n=1470)					< 0.001[a]
SCI	203	13.8	174 (21.5)	29(4.4)	
MCI	517	35.2	277 (34.3)	240 (36.3)	
AD	433	29.5	164 (20.3)	269 (40.6)	
VaD	52	3.5	10 (1.2)	42 (6.3)	
AD/VaD	77	5.2	43 (5.3)	34 (5.1)	
DLB/Parkinson	36	2.4	26 (3.2)	10 (1.5)	
FTD	12	0.8	10 (1.2)	2 (0.3)	
Unspecified dementia	140	9.5	104 (12.9)	36 (5.4)	
Dementia	750	51.0	357 (44.2)	393 (59.4)	<0.001[a]
Depression					
Cornell, score (n=1470)	6.7	5.3	6.5 (5)	6.9 (5.7)	0.71[b]
Previous depression	289	19.7	186 (23)	103 (15.6)	<0.001[a]
Use of antidepressants	232	15.7	125 (15.5)	107 (16.2)	0.39[a]

a= X^2 (Chi square) test, b = Mann-Whitney test, c = t –test, P-ADL = personal activities of daily living, I-ADL = instrumental activities of daily living, MMSE = mini mental state examination, CDT = Clock Drawing Test, SCI = subjective cognitive impairment, MCI = mild cognitive impairment, AD = Alzheimer's disease, VaD = vascular dementia, DLB = Dementia with Lewy Bodies, FTD = frontotemporal dementia

The correlation study (paper III)

Background: The aim of this study was to explore the correlation between the Cornell Scale for Depression in Dementia (CSDD) and the Montgomery-Aasberg Depression Rating Scale (MADRS) among memory clinic patients.

Methods: The CSDD (based on an interview with the caregiver) and the MADRS (based on the patient's opinion) were filled in independently of each other among 520 patients. Principal component and correlation analyses were performed.

Results: The mean score of the CSDD was 7.6 (SD: 6.0), and the mean MADRS score was 9.7 (SD: 6.7). The correlation between the two scales was 0.36 for the whole group, 0.22 in the group with dementia and 0.48 for those without dementia, respectively. Principal component analyses revealed four factors for the CSDD and two factors for the MADRS.

Conclusions: Using two different sources of information, we found a poor correlation between the two scales. We suggest that evaluation of depression among memory clinic patients should be done by interviewing both the patient and the caregiver.

Additional results of sub-study III

In this sub-study, 57.7% of the patients had a CSDD higher than 5. In the principal component analysis (PCA), the four factors accounted for about 49% of the variance for the CSDD. The two factors of the PCA of the MADRS accounted for about 50% of the variance. The correlation between the two scales remained poor even after dividing the sample into different sub-samples and also when comparing the correlating factors of the CSDD and the MADRS according to the two PCAs. However, there were differences between the two memory clinics. These differences are shown in Table 12.

Table 12. Spearman's correlations between the CSDD and the MADRS scores for sub-sample, separated for the two clinics at Oslo University Hospital and Innlandet Hospital Trust

	Total sum scores	Oslo University Hospital (OUS)	Innlandet Hospital Trust (SI)
All patients (n=520)	0.36	0.27	0.58
Women (56.3%)	0.31	0.20	0.59
Men (43.7%)	0.41	0.36	0.51
Age (n=520)			
40-64 (31.7%)	0.31	0.21	0.48
65-75 (36.2%)	0.37	0.33	0.43
76-93 (32.1%)	0.46	0.31	0.79
Years of education (n=506)			
<=8 (30.2%)	0.40	0.23	0.64
>=9 (69.8%)	0.38	0.32	0.55
Marital status (n=510)			
Married (67.8%)	0.43	0.37	0.58
Not married (32.5%)	0.25	0.14	0.59
Diagnosis			
SCI (21.2 %)	0.49	0.38	0.63
MCI (32.5%)	0.47	0.40	0.61
Dementia (46.3%)	0.22	0.16	0.47
MMSE score (n=517)			
3-21 (21.9%)	0.25	0.14	0.55
22-25 (26.5%)	0.35	0.22	0.53
26-28 (29.5%)	0.45	0.41	0.62
29-30 (22.1%)	0.38	0.29	0.62
Clock Drawing Test (n=427)			
Approved	0.41	0.33	0.59
Not approved	0.38	0.24	0.56
Caregiver (n=510)			
Spouse (67.8%)	0.43	0.37	0.55
Others (32.2%)	0.27	0.12	0.64
Relative Stress Scale (RSS) (n=494)			
RSS score below 10 (50.4%)	0.39	0.31	0.56
RSS score above 9 (49.6%)	0.30	0.19	0.64

SCI = subjective cognitive impairment, MCI = mild cognitive impairment, MMSE = Mini Mental State Examination

The cross-cultural study (paper IV)

Background: Different cutoff points for a depressive disorder on depression scales exist in different countries. The reasons could be that the presence or the intensity of the various symptoms on the scales differ. We wanted to explore differences in scores on depression scales among patients in Brazil and Norway.

Methods: The Cornell Scale for Depression in Dementia (CSDD) and the Montgomery–Aasberg Depression Rating Scale (MADRS) were completed independently among 211 elderly outpatients in Brazil and Norway. A psychiatrist, blind to the results, diagnosed depression using the ICD-10 and DSM- IV criteria.

Results: According to the ICD-10 criteria, 29 (33.7%) Brazilian and 51 (40.8%) Norwegian patients had depression (p=0.3). Mean CSDD score was14.4 (SD8.9) in Brazil and 6.8 (SD4.9) in Norway (p<0.001). Mean MADRS score was 13.2 (SD12.1) in Brazil and 8.4 (SD6.8) in Norway (p = 0.02). We analyzed the scores for the depressed and the non-depressed patients separately. In both groups the Brazilian patients had significantly higher scores on both scales compared to the Norwegian patients. In an adjusted linear regression analysis the variable ‘‘country’’ was associated with the CSDD score (beta=-0.29, p=0.01).

Limitations: The protocols in the two countries were not exactly the same. Only one psychiatrist evaluated the patients.

Conclusions: The scores on the MADRS and the CSDD were higher in patients in Brazil than in Norway. In an adjusted linear regression analysis, ‘‘country’’ was the only variable associated with the higher CSDD score.

<u>Additional illustrations for the results of sub-study IV</u>

In sub-study IV, 63.5% of patients had a CSDD score higher than 5. As reported in paper IV, the Brazilian patients had a higher score on nearly every item on the CSDD compared to the Norwegian patients, due mainly to a higher level of severity of each symptom. This was the case among those with and without depression. The only item for which the Norwegian patients had a higher score was for the item “multiple physical complaints.” Figures 6 and 7 show the severity of the various items of the two scales as mean values for the Norwegian and the Brazilian depressed patients (the non-depressed patients are not shown).

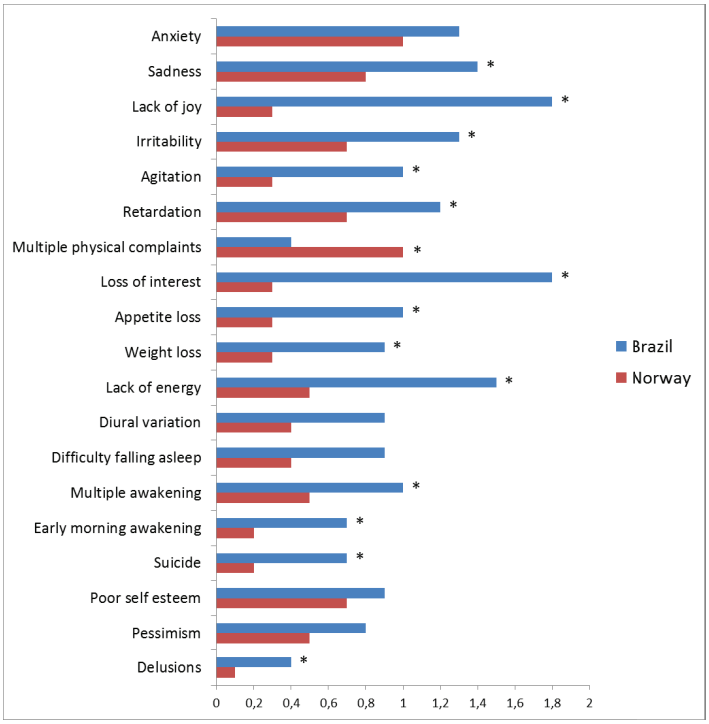

Figure 6. The severity of the various symptoms of depression according to the CSDD in patients with depression in Brazil and Norway (mean values). The * = p< 0.05 between the two groups.

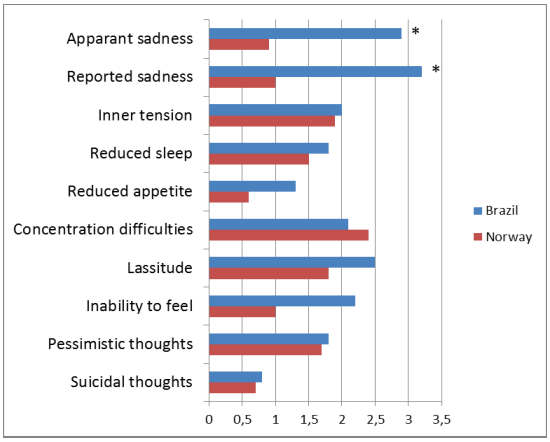

Figure 7. The severity of the various symptoms of depression according to the MADRS in the patients with depression in Brazil and Norway (mean values). The * = p<0.05 between the two groups.

2.8 Discussion

The prevalence of depression

In this study, we found a high prevalence rate of depression according to a clinical diagnosis made by a psychiatrist and of depressive symptoms according to the two screening scales. In the sub-studies (I and IV) where the patients were assessed by psychiatrists, 41% met the ICD-10 criteria for depression in sub-study I, and 38% met those in sub-study IV (33.7% in Brazil, 40.8% in Norway, p=0.3). Using the CSDD to assess depressive symptoms, we found that 54% in sub-study I, 50% in sub-study II, 57.7% in sub-study III, and 63.5% in sub-study IV had a CSDD score higher than 5, indicating depression at the disorder level, according to the results of our validity study (study I). The prevalence rate reported in paper II is possibly too high because we found both in study I and study IV that the prevalence of depression using a clinical diagnosis by a psychiatrist was lower compared to the situation when we used a cut-off point on the CSDD. This may also be the case using other depression scales. However, despite such a discrepancy between a clinical diagnosis of depression and the use of a screening scale to define depression, depression disorders are still very prevalent among people coming to a memory clinic for dementia assessment. Our results are in accordance with other studies that find a high prevalence of depression among patients with cognitive impairment. In a review by Panza, the prevalence of depressive symptoms among patients with MCI varied from 3% to 63% with a median of 34%. The prevalence was higher in hospital-based studies than in population-based studies (Panza et al., 2010). In an outpatient clinic in Argentina, approximately 50% of the patients with AD met the criteria for minor (defined as significant depressive symptomatology) or major depression (Starkstein et al., 2005a), and in a study of elderly Spanish AD patients with a moderate degree of dementia, 38.9% of the patients met the DSM-IV criteria for major depression (Porta-Etessam et al., 2011). Depression is also common among the elderly population without dementia, with the highest prevalence rates seen among the oldest old (Alexopoulos, 2005, Luppa et al., 2012). It is presumed that approximately 20% of the elderly in an elderly population have clinically significant depressive symptoms (Rosenvinge and Rosenvinge, 2003, Alexopoulos, 2005). For this reason, we will recommend the use of a screening scale for depression, and if a high score is obtained on a scale, the physician or psychologist carrying out the dementia assessment should do a further clinical psychiatric interview or refer to a psychiatrist when in doubt about the diagnosis of depression.

In the prevalence study, previous depression, disability in ADL, and younger age were the strongest risk factors for depression. Previous studies have found similar associations (Rosness et al., 2010, Dillon et al., 2011). We also found a higher incidence of depression among patients with dementia other than AD, such as VaD and DLB. This association is found in other studies as well (Ballard et al., 2000, Park et al., 2007). Some studies have shown an association with gender and marital status, with more depressive symptoms among women and the unmarried (Migliorelli et al., 1995, Dillon et al., 2011); however, we could not confirm this in our study. Many of the risk factors are the same for depression in dementia as for depression in the elderly without dementia. Previous depression, disability, and psychosocial adversities are common risk factors in both groups (Cole and Dendukuri, 2003, Dillon et al., 2011). However, depression seems to be more prevalent among the youngest patients with dementia and among the oldest without dementia (Rosness et al., 2010, Luppa et al., 2012).

The correlation between the CSDD and the MADRS

The question, of course, arises as to which screening scale should be recommended and if one should rely on a proxy-rated scale such as the CSDD or an observational scale calling for interviewing the patient, such as the MADRS. The correlation for the two depression scales used in this thesis was poor. In sub-study I, the correlation between the two scales was 0.43 for the whole group, 0.48 for the patients with dementia, and 0.44 for those without dementia. The correlation was poorest among those with dementia, and slightly better among those less cognitively impaired. In sub-study III, we found, a bit surprisingly, that the correlation between the score of the two scales was influenced by the location of the memory clinic. The memory clinic at Innlandet Hospital Trust (SI) is affiliated with a department of old age psychiatry, and there are few personnel involved in completing the scales. By contrast, the memory clinic at Oslo University Hospital (OUS) is part of the geriatric department, and many nurses and physicians have been involved in completing the scales over the past years. It might be that the correlation was consequently much lower at OUS because of these differences between the two clinics. However, we do not know if the affiliation (psychiatry or geriatric medicine) is of more importance, or the fact that few or many nurses and doctors were involved in applying the scales. Most probably the affiliation is more important (see Table 13).

Previous studies have found that patients tend to underreport and that caregivers tend to overreport depressive symptoms (Snow et al., 2005). In sub-studies I and IV, we reported a

higher prevalence rate of depression using the CSDD and could, therefore, confirm the findings of previous studies. We could not confirm, however, that the prevalence rate is lower when interviewing the patients using the MADRS. Using the best cutoff-point on the MADRS, the prevalence rate was as high as using the CSDD (papers I and IV).

Only a few studies have compared the scores on both the CSDD and the MADRS in the same group of patients. Müller-Thomsen et al. found a correlation of r = 0.93 between the scores on the two scales among patients with mild AD and a correlation of r = 0.76 among those with severe dementia. In this study, the scales were completed independently by well-educated health care personnel but not validated against a clinical diagnosis of depression (Muller-Thomsen et al., 2005). Leontjevas et al. also found a high correlation between the scores on the two scales (r = 0.76), but in this study the scales were not completed independently of each other (Leontjevas et al., 2009).

When assessing patients for depression, it is important to keep in mind that factors such as clinical setting, educational level of the interviewer, and cultural setting influence the results of the scales. Therefore, depression scales should be interpreted with caution.

Validity of the CSDD and the MADRS

Given the poor correlation between the two scales, their validities should be discussed.

The Cornell Scale for Depression in Dementia (CSDD)

In the original publication by Alexopoulos, the group with minor depression according to the Research Diagnostic Criteria (RDC) had a mean CSDD score of 7.7 (SD: 2.5). In the group identified as having major depressive disorder, the mean score was 12.6 (SD: 2.6). However, no receiver-operating characteristic (ROC) analysis with optimal cut-off point was made, and in spite of this, a score between 8 and 12 (above 7) was suggested for mild depression in persons with dementia and a score higher than 12 (13+) was suggested for moderate or severe depression (Alexopoulos et al., 1988a). The values 8 and 12 have been used often as cut-off points in many studies. The CSDD has been validated in many different settings using different diagnostic criteria. However, among patients with dementia, validity studies have shown different cut-off points, from the lowest at 4/5 in Denmark and Japan, to the highest at 12/13 in Brazil and China, whereas other studies have achieved results closer to the mean values of the original study (Schreiner et al., 2003, Lam et al., 2004, Korner et al., 2006, Barca et al., 2010b, Lim et al., 2012, Portugal et al., 2012).

Both the persons who administer the CSDD and the informants who provide the information about depressive symptoms may influence its result. In the Danish study, geriatric psychiatrists completed the CSDD based on information provided by the patients and the caregivers (Korner et al., 2006). In a study done in the US by Watson et al., the scales were completed by nursing assistants (Watson et al., 2009). These patients were in residential care and may therefore have had a lower functional status than the outpatients in the Danish study. Teresi in the US found a low recognition rate of depression when nursing-home staff completed the CSDD and other screening tools. A psychiatrist diagnosed depression in 44% of the cases, nursing aides recognized depression in 32% of the patients, nurses in 29%, and social workers recognized depression in 20% of the patients (Teresi et al., 2001). These results are in contrast to the results of the present thesis, and one could suggest that the clinical experience of the interviewer may play an important role. In the study by Teresi, the less-experienced social workers detected fewer patients with depression using the CSDD.

Despite the differences between the two groups in sub-study II regarding gender and age, comorbidity, and cognition, the mean score on the CSDD was the same. The patients examined in our study were all living at home. With increasing cognitive impairment, some symptoms of depression will overlap more with the symptoms of dementia, which may explain the higher cut-off points found in the Norwegian nursing-home study compared to the present study (Barca et al., 2010b).

In the original study by Alexopolous, the CSDD was proven effective to detect depression in people without dementia as well (Alexopoulos et al., 1988b). In a study by Engedal, the CSDD was completed among elderly persons without dementia, and it was found to be less suitable with poorer discriminatory power than the MADRS (Engedal et al., 2012b). In the present study (I), no difference was found between those with and without dementia. However, we still believe that the severity of dementia may influence the validity of the CSDD. In the Brazilian study by Portugal et al., it was demonstrated that the CSDD better discriminated depressed from non-depressed patients among those with mild dementia compared with patients with moderate or severe dementia (Portugal et al., 2012).

As found in sub-study IV, cultural differences will also influence how the CSDD is completed. Higher scores and higher intensity of the symptoms present were found in Brazil than in Norway. This was found among those both with and without depression, which causes us to presume that this is due to cultural differences.

Karim et al. found differences in CSDD scores among patients with AD in Pakistan and the UK (Karim et al., 2011). The scores were higher in Pakistan than in the UK. The mean score in the UK was 5.0 (SD 3.1), and 62% had a score below 6. In Pakistan, the mean score was 14.4 (SD 5.2), and 67% had a score between 10 and 18. However, the results were not validated against a clinical diagnosis. Shah et al. did not, however, find similar differences in the CSDD between patients with dementia in Korea and the UK (Shah et al., 2004).

The most surprising finding in the cross-cultural study (IV) was that the Norwegians had a higher score on the item "multiple physical complaints." This is probably explained by the fact that the Norwegian population in general reports more chronic pain than the populations of all other European countries (Breivik et al., 2006). It may be more acceptable for Norwegians to report pain instead of depressive symptoms. It is known that chronic pain is related to sleep problems and psychiatric symptoms (Nielsen et al., 2010). Another Norwegian study using the CSDD among patients with AD, also found a strong association between multiple physical complaints and depression (Engedal et al., 2011).

Another surprising finding in our study was that the Norwegian caregivers reported a greater burden than the Brazilian caregivers, despite the fact that the Norwegian patients were less cognitively impaired, and that the public social and health care services are more highly developed in Norway than in Brazil. This may, however, also lead to higher expectations among caregivers in Norway.

Different reference standards may influence the cut-off point. When using the ICD-10 criteria, more patients are classified as being depressed than when using the DSM-IV criteria, and even more are classified as depressed when the PDC-dAD is used. In the Norwegian validity study of the CSDD among nursing-home patients, a lower cut-off was found when using the ICD-10 versus the DSM-IV criteria.

The degree of dementia did not influence the CSDD scores in the cross-cultural comparison between Brazil and Norway. We did, however, use different diagnostic criteria concerning dementia diagnoses. In Brazil, the DSM-IV criteria were used; in Norway, the ICD-10 criteria were used. It has been claimed that the ICD-10 criteria have a lower detection rate for dementia than the DSM-IV criteria, but a Norwegian study among patients in a geriatric outpatient clinic did not find any discrepancy between the two sets of diagnostic criteria (Naik

and Nygaard, 2008). We do not believe that the use of different criteria for dementia has influenced the results in our study.

Montgomery-Aasberg Depression Rating Scale

The MADRS is less validated among the elderly and patients with cognitive impairment. In our study, we found that the MADRS better distinguishes depressed from non-depressed patients, including those with moderate dementia, compared to the CSDD. In the study by Portugal et al., the MADRS also performed better than the CSDD (Portugal et al., 2012). Leontjevas et al. have conducted two validity studies of the CSDD and the MADRS among nursing-home patients (Leontjevas et al., 2009, Leontjevas et al., 2012). The first, a small-scale study including 63 patients, was carried out among patients with early onset dementia (mean age 58.7 years, SD: 6.4), and the second one, including 101 patients, was conducted among older patients (mean age 83.8 years, SD: 6.4). In both studies, the MADRS and the CSDD were completed based on one (and the same) interview with a professional caregiver (licensed practical nurse). The interviewer was either a psychologist or a psychology student. In some cases, the clinical diagnosis of depression was made by an elder-care physician and a psychologist, who were "not blinded" for the results of the two scales. Among the 63 patients (nine with depression) with early onset dementia, a MADRS cut-off >14 achieved a sensitivity of 67% and a specificity of 92%. A MADRS cut-off score of 19/20 yielded the highest sum of sensitivity, 75%, and specificity, 84% (Leontjevas et al., 2009). Among the older patients, the best cut-off point was 13/14 (sensitivity of 78% and specificity of 66%) (Leontjevas et al., 2012). Leontjevas found that the MADRS had less discriminatory power to distinguish depressed from non-depressed patients with increasing severity of dementia. The negative predictive value was high and the positive predictive value was low for both scales. Although the two studies by Leontjevas et al. included few depressed patients and they did not follow the rule outlined by Sackett about "blindness" (Sackett et al., 2000), it seems that the age of the patients had some influence on the best cut-off point on the MADRS, as the cut-off was lower for the oldest patients. This is in accordance with our cross-cultural study (IV), where the younger patients had higher scores than the older patients. This finding was significant for the Norwegian sample. The variable "country", however, did not influence the MADRS score.

Only a few validation studies of the MADRS have been performed among older patients without dementia. They have resulted in different "best" cut-off points as well. In these studies, better concordance with the clinical diagnoses is achieved, which could indicate that

the severity of dementia or cognitive impairment may lead to less-valid results. In a study by Engedal et al., the best cut-off for a depressive disorder with a DSM-IV diagnosis of depression was 16/17 (Engedal et al., 2012b). In another study, patients were screened for entry in a medical trial, and an optimal cut-off point of 20/21 was found (Mottram et al., 2000). There were no differences between the younger and the older patients in this study (mean age 77.2 years, SD: 7.9) or between genders. However, no clinical diagnosis was made. The reference standard was semi-structured instruments for assessments of psychiatric syndromes in the elderly (GMS/AGECAT), which make this study less valid from an evidence-based medical perspective. Taking all studies together, the MADRS produced better validity results than the CSDD and should be preferred for use with patients without dementia, but it is less useful with increasing severity of dementia with lower sensitivity and specificity (Leontjevas et al., 2009, Portugal et al., 2012, Knapskog et al., 2011).

Studies have also been conducted among stroke patients (Sagen et al., 2009) and among patients with Parkinson's disease but no dementia (Leentjens et al., 2000, Silberman et al., 2006, Reijnders et al., 2010), resulting in cut-off points between 8/9 (Sagen et al., 2009) and 14/15 (Leentjens et al., 2000). Patients with Parkinson's disease have more somatic symptoms and fatigue that could have influenced the results. However, in only one of these studies (Silberman et al., 2006) were the strict rules outlined by Sackett concerning "critical appraisal" followed, which make the results of the other studies less valid.

2.9 Methodological considerations

Limitations

There are some limitations to this study. Depression was diagnosed by only one psychiatrist in the validity study (I) and the cross-cultural study (IV). The quality of sub-studies I and IV would have been improved if two or more psychiatrists had examined the patients independently before making the diagnosis of depression, and if the psychiatrist could have interviewed a caregiver (not involved in the CSDD interview) in addition to the patient. Another limitation in the cross-cultural study was that the protocols in the two countries were not exactly the same. We used different scales to assess caregiver burden and ADL functioning, but we do not think that this influenced the main results. Another factor that could have influenced the results was how the psychiatrists in the two countries interpreted the presence of depressive symptoms and diagnosed a depressive disorder according to the

criteria of DSM-IV and ICD-10. We tried to minimize this possible bias by discussing the use of the diagnostic criteria several times during the study period. In addition, one of the psychiatrists in Norway (MLB) is a Brazilian who speaks Norwegian fluently. She ensured that the symptoms in the diagnostic examination were interpreted in the same way.

The quality of the prevalence study (II) and the correlations study (III) would have been improved if we had had the possibility to use a psychiatrist's diagnosis of depression with standardized criteria for depression, such as the ICD-10 or the DSM-IV. In the prevalence study, we used the CSDD to define depression. By using three different cut-off points for a depressive disorder, different prevalence rates were, of course, achieved.

In the prevalence study (II), we could not include all the patients referred for dementia assessment in the memory and outpatient clinics. Of the patients included in the common register in the southern part of Norway, about 80% had the CSDD completed by a caregiver. Nevertheless, we consider our results on the CSDD to be representative for the patients who came to the two major memory clinics at OUS and SI because the inclusion rate in the register was 90% at these two clinics. The majority of the patients in the present study came from these two clinics. As we have no information on the participation rate of the 10 other clinics, we cannot be certain that the results are representative of all patients coming for dementia assessment in these specialist health care clinics in Norway. However, as the mean CSDD scores did not differ among the patients of the various clinics and also the rate of depression using the two lowest cut-off points did not differ, we assume that it is not unlikely that our results are valid for all patients coming to specialist health care services for dementia assessment in Norway.

Strengths

The strengths of the study were that we filled in the scales independently of each other and that the diagnoses of depression by a psychiatrist in sub-studies I and IV were made without knowledge of the results of the CSDD and the MADRS evaluations. To the best of our knowledge, this was the first validity study comparing the CSDD with the MADRS, both blinded for a psychiatric assessment, in a memory clinic population. Another strength of the validity study was that we used the criteria of Sackett et al. [31] for "critical appraisal" regarding diagnostic tests. Most of the patients were recruited using no selection criteria, and they were all assessed in a comprehensive manner.

The analyses of factors associated with depression resulted in very similar results using the three different cut-off points for depression. The validity of these results could, therefore, be seen as solid and a strength of the analysis in sub-study II.

2.10 Clinical implications

Regardless of clinical diagnosis by a trained psychiatrist or through the use of screening scales for depression, we found that depression was very common among patients coming for a dementia assessment. This should have implications for clinical practice, as we would recommend that screening for depression be made part of a standardized dementia work-up whether or not the patients or the caregivers complain about depressive symptoms. Depression may lead to poorer quality of life, and in some patients, it might, together with other factors, predispose them to a faster progression of the dementia disorder. Treatment exists and should be prescribed.

We do not believe that every patient who sees a doctor for a dementia assessment should be examined by a psychiatrist; that would be too time-consuming. The question, therefore, arises about which screening scales should be recommended. On one hand, as seen in this thesis both CSDD and MADRS could be used; but on the other hand, we have demonstrated that the correlation between the two is poor. Whenever possible, we would recommend that clinicians use both a proxy-rated scale and an observation scale by interviewing the patients. The clinician should have access to the results of both and should make a decision about the diagnosis of depression using all the available information from both kinds of scales and her/his own impression during the consultation.

We have also shown that cultural differences influence the results of using scales. The result of our sub-study IV illustrates how important it is to validate a scale before using it in a different culture than the one for which it was developed. We found this to be especially true when proxy-based information was used.

2.11 Proposals for future research

Even though we found a high prevalence rate of depression diagnosed by a psychiatrist in our study, this needs to be confirmed in a larger study among memory clinic patients. As one of the most prevalent behavioral and psychological symptoms in dementia, depression occurs in

approximately 50% of patients during the course of the dementia disorder (Starkstein et al., 2005a). We would expect a high prevalence rate to be found in a future study as well.

If the high prevalence rate is confirmed, efforts should be made to expand knowledge about causality. Is depression among this group of patients caused by psychological mechanisms and the lack of coping strategies, and/or do biological changes play an important role? Increased prevalence of depression has been found among patients with subcortical neurodegeneration and is associated with frontostriatal dysfunction (Alexopoulos et al., 2005). There is an increased focus on the role of neuroinflammation in both depression and dementia because many of the same structural changes in the brain are found in both conditions. Many of the same inflammatory processes also are found in both conditions, indicating an interaction between depression and dementia (Leonard, 2007). This interaction should be explored in further studies.

In addition, psychological adversities may contribute to the development of depression in the elderly. A strong correlation between depressive symptoms among elderly people and their feelings about control in their lives has been reported (Bjorklof et al., 2013). Coping mechanism and coping resources are important in the prevention of depression and thus should be given more attention.

There is a discrepancy concerning the effect of treatment for depression in dementia and whether treatment can influence the prognosis of dementia. The documentation of the effect of treatment is poor (Lyketsos and Lee, 2004), but this does not necessarily mean that there is no effect. Treatment studies are characterized by a large amount of heterogeneity in both the use of various methods to assess effects and in how to intervene. Few studies are of acceptable quality (Regan and Varanelli, 2013). However, lifestyle and pharmacological interventions may have considerable impact on reducing depression in dementia, or at least postponing the onset of dementia (Kivipelto and Solomon, 2008). Higher mortality is found among patients with comorbid depression (Barca et al., 2010a), and the risk of being admitted to institutional care increases (Starkstein et al., 2008). Better treatment strategies would have a large impact on the prognosis of dementia, and different treatment strategies should be explored in the future.

2.12 Conclusion

The prevalence of depressive symptoms and depression was high among memory clinic patients in this study. The strongest factors associated with depressive symptoms were younger age, ADL impairment, and previous incidence of depression. Both the CSDD and the MADRS were suitable as screening tools. According to the ROC analyses, the MADRS was slightly better at distinguishing depressed from non-depressed patients. The correlation between the two scales was poor when they were completed independently of each other from two different sources of information. However, the two scales can provide different information about depressive symptoms in patients with memory problems and dementia. We suggest that evaluation of depression among memory clinic patients should be done by interviewing both the patient and the caregiver. We found greater cross-cultural variability using the CSDD compared to the use of the MADRS, and the scores on both scales were significantly higher among the Brazilian non-depressed and depressed patients compared to the Norwegian patients with and without depression, even though the prevalence of depression was the same in the patients of the two samples. The Norwegian patients had a higher score on only one item of the Cornell scale, namely on ‘‘multiple physical complaints.’’ Proxy-rated scales such as the CSDD scales should be validated in the country where they will be applied.

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I

II

III

IV

Errata

Paper II.

The title should be:

Prevalence of depression among memory clinic patients as measured by the Cornell Scale for Depression in Dementia